ETHICAL ISSUES IN POSTAUTHORIZATION DRUG TRIALS

Rosemarie de la Cruz Bernabe

The studies presented in this thesis were performed in the context of the Escher project (T6-202), a project of the Dutch Top Institute Pharma.

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ETHICAL ISSUES IN POSTAUTHORIZATION DRUG TRIALS

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Chapter 2

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Chapter 3

RD Bernabe, GJ van Thiel, JA Raaijmakers, and JJ van Delden. Is informed consent necessary for randomized Phase IV 'observational' drug studies? *Drug Discov.Today* 16 (17-18):751-754, 2011.

Chapter 4

RD Bernabe*, F H van der Baan*, AL Bredenoord, JG Gregoor, G Meynen, M.J Knol, and GJ van Thiel. Consent in psychiatric biobanks for pharmacogenetic research. *Int.J.Neuropsychopharmacol.* :1-6, 2012.

Chapter 5

RD Bernabe, G.J van Thiel, JA Raaijmakers, and J J van Delden. The need to explicate the ethical evaluation tools to avoid ethical inflation. *Am.J.Bioeth.* 9 (11):56-58, 2009.

Chapter 6

RD Bernabe, G.J van Thiel, J A Raaijmakers, and J J van Delden. The risk-benefit task of research ethics committees: an evaluation of current approaches and the need to incorporate decision studies methods. *BMC.Med.Ethics* 13:6, 2012.

Chapter 7

RD Bernabe, GJ van Thiel, JA Raaijmakers, and JJ van Delden. Decision theory and the evaluation of risks and benefits of clinical trials. *Drug Discov.Today* 17 (23-24):1263-1269, 2012.

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RD Bernabe*, G Wangge*, MJ Knol, OH Klungel, JJ van Delden, A de Boer, AW Hoes, JA Raaijmakers, GJMW van Thiel. Phase IV non-inferiority trials and additional claims of benefit. Submitted.

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Chapter 1

GENERAL INTRODUCTION

I. Barriers to drug innovation and the TI Pharma Escher project

The pharmaceutical community has been facing the challenge of increased research and development spending and decreased output of new molecular entities. The problem is best encapsulated by the WHO Priority Medicines for Europe and the World:

> Worrying trends have emerged which suggest that the time needed to bring a product to market is increasing, the number of new product launches is decreasing, and the cost of developing a new chemical entity as a medicine continues to increase. Many pharmaceutical projects in the early stages of research and development never make it through the "pipeline", so that the translation from basic science to applied product development has become a weak link (1).

In 2006, the US Congress report entitled, *Research and Development in the Pharmaceutical Industry* echoed these WHO findings (2). In Figure 1, we see the inverse relationship between spending and pharmaceutical output: there is increased R&D spending while drug productivity declines.

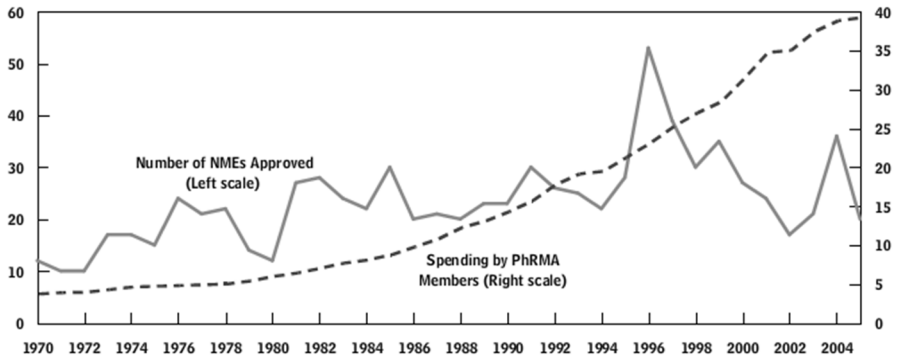

Figure 1: New molecular entities approvals and pharmaceutical companies' spending on R&D (in Billions of US dollars) (2)

Hence, since the early 2000's to the present, much effort has been put to remove barriers to drug innovation: efforts ranged from increased collaboration, the conceptualization of new clinical trial methodologies, regulatory changes, the reconceptualization of the business strategies of pharmaceutical companies, to active

efforts to make the drug development process shorter and ideally more safe and effective.

Within the Dutch environment, the Top Institute Pharma, itself a collaboration of the government, academia, and the pharmaceutical industry, contributed appreciably through its various research projects. One of the missions of TI Pharma is to "create, through synergy, excellence in groundbreaking, cross-disciplinary research, within the framework of Priority Medicines" (3). Within the ambit of this mission, TI Pharma created the Escher Project, a relatively large research project composed of 16 PhD projects meant to "identify, evaluate and remove regulatory bottlenecks hampering the efficiency in pharmaceutical innovation and stimulate factors helping innovation" (4). The projects were then strategically divided into three research areas: "regulatory barriers and opportunities in drug innovation; innovative models of testing, and monitoring efficacy and safety of new drugs; and knowledge management, learning and education"(4). Within the first research area is the Ethics and Society cluster, which is meant to look at ethical and societal issues that affect access to innovative drugs and to set an agenda on how to overcome certain ethical and societal issues. Within this cluster is Escher project 2.8.

II. Project 2.8

Project 2.8 aims to make explicit and as much as possible provide responses to the ethical issues in late phase trials.

Late phase trials, especially phase IV trials, have traditionally not received as much attention as the other phases. For some time, phase IV trials were almost equated to studies that were not as rigorous as the other phases, and may even be coated marketing stints to promote a new drug. These were back then termed, "seeding trials".

However, things have changed. Recently, the number of phase IV studies increased (5). In ClinicalTrials.gov, the number of yearly registered phase IV studies since 2005 has consistently been >1539, a dramatic increase from the <73 registered phase IV trials every year from 2000 to 2004[1]. This trend may be accounted for by the following:

A. Emphasis on post-authorization requirements and commitments

Even after drug authorization, continued studies on a drug are necessary for reasons such as new or additional information on drug-drug interaction and dose-response;

[1] We did a search in ClinicalTrials.gov on December 17, 2012 of all clinical trials that were registered from the year 2000 to the year 2011 with the following results (in chronological order, starting from the year 2000): 29, 32, 70, 51, 72, 1939, 1540, 1684, 2093, 1850, 1838, 1794.

safety issues that are apparent only in large populations and/or over time; efficacy of the drug on a subpopulation; and others. Such post-authorization data are needed for the continuous risk-benefit assessment of a drug. Due to the necessity of these data, both the European Commission and the US Food and Drug Administration enforced wider regulations on post-authorization commitments.

In 2006, the European Commission, through the document, *Volume 2A Procedures for Marketing Authorization, Chapter 4 Centralized Procedure*, specified two types of post-authorization commitments: specific obligations and follow-up measures. Specific obligations are mandatory studies for drugs that have been authorized under special circumstances, notably due to their limited efficacy and/or safety data at the time of authorization (6;7). These obligations form the bases of the yearly reassessment of the drug. Follow-up measures, on the other hand, are commitments that may be required independent of the type of authorization, i.e., whether the authorization was granted under special circumstances or not (6;7).

The FDA, in response to previous studies that showed low compliance to post-authorization commitments (8), enforced the *Food and Drug Administration Amendments Act* in 2007. This act gave broader post-authorization powers to the FDA including the differentiation of FDA's authority to impose a postmarketing requirement as opposed to its authority to request for postmarketing commitments. The acceptance of a postmarketing requirement by the marketing authorization applicant is a condition for approval. These requirements are meant to "assess a known serious risk related to use of the drug; assess signals of serious risk related to the use of the drug; or, identify an unexpected serious risk when available data indicate the potential of a serious risk" (9). In its expanded form, the FDA may now impose such requirements beyond the scope of accelerated approvals or pediatric research (9). Postmarketing commitments, on the other hand, are studies that the FDA requests from the marketing authorization holder that are meant to "gather additional information about product safety, efficacy, or optimal use"(9). The information from these commitments may be important or useful; nevertheless, the gathering of such information is not a necessary condition for drug approval (9).

Hence, both in the USA and in the EU, there is regulatory force to conduct phase IV studies.

B. Voluntary phase IV studies

Apart from regulatory requirement, pharmaceutical companies have increasingly initiated phase IV studies. According to a Cutting Edge Information survey, among the postmarketing trials of the surveyed companies, 82% are self-initiated while the remaining are postmarketing commitments/requirements. This is an increase from

the 61% of voluntary phase IV studies in 2006 (10). This increase in voluntary phase IV studies may be accounted for by the need for a competitive edge in terms of reimbursement (10), which is in line with the increased emphasis on the need for relative effectiveness data, i.e., data on "the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice" (11;12).

Hence, phase IV studies increased due to the need for continuous benefit-risk data, regulatory requirements, and reimbursement concerns. However, with increased phase IV studies are ethical issues as well. In 2008, van Thiel and van Delden outlined the ethical issues that come with phase IV studies that support innovation:

> …a main source of ethical concern is the mix of medical research and clinical practice in this post registration phase. Problematic aspects are related to voluntariness, informed consent, risk management, conflicts of interest and the responsibilities of the physician in shaping a high principled research practice (13).

III. Ethical issues in phase IV

In their article, van Thiel and van Delden classified the ethical issues in phase IV by using two research ethics paradigms: the protection paradigm and the distributive justice paradigm (13). Within the first paradigm they placed the issues on informed consent, voluntariness and protection against risk (13). Then, within the distributive justice paradigm, they placed the problems on selection bias and neglect (13). In this thesis, we interpret the two paradigms not as mutually exclusive nor opposing paradigms. We also do not assume that one paradigm is better compared to the other. Instead, it seems logical to see the two paradigms as interdependent: the issues addressed by the protection paradigm are fundamental issues in research ethics while the issues addressed by the distributive justice paradigm are social context-infused issues; hence, a clarification of the fundamental issues is necessary before any meaningful discussion on context-infused issues are possible; but, social context-infused issues allow for the concretization of these fundamental issues.

A. Protection paradigm issues

The ethical issues surrounding robust phase IV studies straddle within the tension between safety and immediate access. This tension is the thread that runs across the various phase IV concerns: novel trial designs that aim for quicker access ought to be complemented with scientifically thriving phase IV studies that provide an updated

risk-benefit profile of a drug. Concretely, in ethics, this would mean addressing fundamental matters such as ethically assessing the benefits and the risks of such studies; exploring the issue of when a waiver of informed consent may be ethically justifiable for the purpose of facilitating research; making explicit what characteristics of phase IV studies are ethically relevant; or, issues whether physician-researchers have a therapeutic obligation to patient-physicians in these studies. These are fundamental ethical questions in phase IV, i.e., these are ethical questions for phase IV studies in general, questions that do not need to situate phase IV within the various socio-economic contexts. These fundamental issues fall within the protection paradigm, i.e., issues on informed consent, voluntariness, and protection against risk.

B. Distributive justice paradigm issues

Beyond the fundamental ethical issues of the protection paradigm are phase IV issues within the multifarious socio-economic contexts. Hence, the distributive justice paradigm is concerned with questions of selection bias and neglect such as the issue of justice and fairness in the choice of patient-participants in phase IV; the dilemma on the off-shoring of phase IV research while the 10/90 gap persists, i.e., the just distribution of benefits and burdens; cultural nuances and the appropriateness of informed consent forms and procedures, etcetera. All these issues assume inequality in the world and hence the necessity of taking nuances into consideration when reflecting on the contextual ethical issues in phase IV. Simply put, these are all issues of just allocation within the various socio-economic contexts of phase IV studies.

While acknowledging that the ethical issues in both paradigms are urgent and important, this thesis will be limited to the fundamental ethical issues within the protection paradigm.

IV. Structure of the thesis

Within the protection paradigm, we address the following issues:

A. Informed consent in late phase trials

The gathering of informed consent is a widely accepted ethical necessity for the inclusion of participants in a trial. However, there have been concerns that in large phase IV trials, informed consent may be a source of bias or is too burdensome. As such, we ask the question, “When, if at all, may informed consent be waived in phase IV? Admittedly, there is a variety of phase IV studies in terms of design and purpose. As such, it would be practical to situate this question within workable themes:

1. *Chapter 2* positions the question of waiving of informed consent within the framework of non-interventional phase IV trials;
2. *Chapter 3* looks at the issue of the necessity of informed consent in randomized phase IV drug trials;
3. *Chapter 4* situates this question within psychiatric biobanks for pharmacogenetic research.

B. Benefit-risk assessment

The assessment of the benefits and the risks of drugs is currently one area that the EMA and FDA have been working on (14;15). Indeed, a transparent and efficient assessment of benefits and risks would greatly aid in decision-making, whether it is in providing marketing authorization, in recalling drugs, or in allowing drug trials. In ethical deliberation and decision-making on the acceptability of clinical trials, the assessment of benefits and risks is also a requirement. In spite of the necessity of benefit-risk assessment in ethical deliberation, there are no tools or guidelines on how to go about it. We wish to respond to this lack by showing how decision theory and risk studies may be used in evaluating the ethical acceptability of clinical trials.

1. In *Chapter 5*, we shall raise the issue of the need for ethical evaluation tools for the purposes of clarity and reasonableness in benefit-risk assessment;
2. In *Chapter 6* we shall evaluate the current methods used to assess benefits and risks and argue for the need to incorporate decision studies methods; and
3. *Chapter 7* spells out how the assessment of a trial's benefits and risks may be done using decision theory.

C. Therapeutic orientation of phase IV

Compared to the other phases, phase IV trials take place within the context of clinical practice, where patients are primarily looking for treatment. As such, the ethical requirements in terms of study design, purpose, methodology, and attitude towards patient-participants must also be different.

1. In *Chapter 8*, we shall look at empirical data on noninterventional phase IV studies and raise the importance of additional benefit claims of these studies precisely because of the assumed clinical value of these studies, i.e., the therapeutic orientation of phase IV; and
2. In *Chapter 9*, we shall assume the merging of therapy and practice in phase IV; rather, we wrestle with the question on the therapeutic obligation of physician-researchers to patient-participants in phase IV.

Reference List

(1) Kaplan, W. and Laing, R. Priority medicines for Europe and the world. World Health Organization; 2004 Nov.

(2) US Congressional Budget Office. Research and development in the pharmaceutical industry. 2006 Jan 10.

(3) Dutch Top Institute Pharma. Mission of TI Pharma. Dutch Top Institute Pharma 2012; Available from: URL: http://www.tipharma.com/about-our-institute/our-mission.html

(4) Dutch Top Institute Pharma. The Escher Project. Dutch Top Institute Pharma 2012;Available from: URL: http://www.tipharma.com/pharmaceutical-research-projects/drug-discovery-development-and-utilisation/escher-project.html

(5) Brower A. Phase 4 research grows despite lack of FDA oversight. Biotechnol Healthc 2007 October;4(5):16-22.

(6) European Commission. Volume 2A Procedures for marketing authorization, Chapter 4 Centralized procedure. 2006.

(7) European Medicines Agency. European Medicines Agency post-authorisation procedural advice for users of the centralised procedure. 2012. 10-12-2012.

(8) US FDA. Report to Congress: reports on postmarketing studies. 2002.

(9) Institute of Medicine. Ethical and scientific issues in studying the safety of approved drugs. Washington, D.C.: National Academies Press; 2012.

(10) Cutting Edge Information. Pharma companies increase voluntarily initiated phase IV trials by 21%. Business Wire 2012 November 8;Available from: URL: http://www.businesswire.com/news/home/20121108005017/en/Pharma-Companies-Increase-Voluntarily-Initiated-Phase-IV

(11) European Commission. Core principles on relative effectiveness. 2008.

(12) Eichler HG, Bloechl-Daum B, Abadie E, Barnett D, Konig F, Pearson S. Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers. Nat Rev Drug Discov 2010 April;9(4):277-91.

(13) van Thiel GJ, van Delden JJ. Phase IV research: innovation in need of ethics. J Med Ethics 2008 June;34(6):415-6.

(14) European Medicines Agency. Benefit-risk methodology project. 2012.

(15) US FDA. Enhancing benefit-risk assessment in regulatory decision-making. US FDA 2012 November 20;Available from: URL: http://www.fda.gov/ForIndustry/UserFees/PrescriptionDrugUserFee/ucm326192.htm

PART I:

INFORMED CONSENT IN PHASE IV

Chapter 2

INFORMED CONSENT AND PHASE IV NON-INTERVENTIONAL DRUG RESEARCH

RDC Bernabe, GJMW van Thiel, JAN Raaijmakers, and JJM van Delden. Informed consent and phase IV non-interventional drug research. Current Medical Research & Opinion 27 (3):513-518, 2011.

Abstract

Most of the literature on informed consent in pharmaceutical drug research works on the assumption that informed consent is something that is homogeneous and thus can be rendered procedurally universal. This may be justifiable to a certain extent owing to the fact that these are all drug trials anyway. Nevertheless, in spite of this general similarity, we also know that the clinical drug development phases are characteristically different, and that phase IV is very different from the other phases because, owing to its postmarketing nature, it is much more varied in scope and in type. Thus, it is worthwhile looking into the ethical nuances relevant to the informed consent process in phase IV non-interventional drug research. We shall deal with the issues on the necessity of informed consent for this type of research and then discuss the possibilities for an opt-out system. We conclude that informed consent is necessary for non-interventional studies, and thus any form of waiving of rights of participants to informed consent must have a valid substantial justification. The distinct character of phase IV accounts for the difference in content of the informed consent document compared to that of earlier phases, and both opt-in and opt-out procedures are ethically justifiable as long as the participant's participation remains informed and voluntary.

I. Introduction

There is a vast body of literature about informed consent in research, although most of this literature is based on the assumption that informed consent ought to be something that has uniform application. As such, when informed consent in research is talked about, it is assumed that what applies in a phase I dose tolerance study should also be applicable to a phase IV comparative effectiveness study. To a certain extent this is justified by the fact that both are phases of drug development, and thus trial participants are all taking part for the primary purpose of contributing to the furthering of knowledge about a drug that may benefit future patients. Nevertheless, in spite of this general similarity, it is also known that clinical drug development phases are characteristically different (1). Phase IV is very much different from the other phases owing to its postmarketing nature – it is much more varied in scope and in type. There are many types of a phase IV trial, and the comprehensive definition of the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) refers to the enormity and heterogeneity of this phase:

> … all studies (other than routine surveillance) performed after drug approval and related to the approved indication … Commonly conducted studies include drug–drug interaction, dose-response or safety studies and studies designed to support use under the approved indication, e.g. mortality/morbidity studies, epidemiological studies (1).

As such, the heterogeneity, the scale, and the huge variation present in phase IV would intuitively tell us that though participants may all be "consenting" to the universal goal of drug trials, the multifaceted and postmarketing nature of phase IV sets it aside as a special case. Thus, how informed consent particularly applies to phase IV may be radically different to how it applies to the earlier phases, even if the original essence of it remains the same, i.e., to uphold the "respect for persons" (2) by safeguarding their autonomy and protecting them from risks (2). Or, in Mansson and O'Neill's terms, informed consent ensures that participants are not "abused, manipulated or undermined, or wronged" (3).

Since it is presumptuous to speak about informed consent in phase IV as if it were homogeneous, it would be best to look into specific types of phase IV, and discuss them individually. In this chapter, we shall look into the ethical issues and the application of informed consent in phase IV non-randomized, non-interventional, not data-only studies. The need to look into the nuances of late-phase trials is highlighted in the current European Medicines Agency *Road Map to 2015* draft in relation to the goal of "maximizing the value of information generated in the post-authorization

phase" (4) as this is valuable for both conditional marketing authorization and post-authorization follow-ups (4).

To address the main topic of concern, we shall first look into the definition of a non-interventional study. Then we shall deal with the issues on the necessity of informed consent for this type of research. Lastly, we shall proceed to the question of what sort of informed consent procedure may be ethically justifiable.

II. What is a non-interventional study[2] (NIS)?

What is an NIS? Directive 2001/20/EC article 2 (5) defines a non-interventional trial in the following manner:

> A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization. The assignment of the patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients and epidemiological methods shall be used for the analysis of collected data.

Thus, by NIS we refer to an observational study of marketed drug/s that is/are prescribed in accordance with their marketing authorization. This means that the trial protocol does not in principle affect the prescription practice and the diagnostic tests fall within regular clinical procedures. Questionnaires, interviews, and blood samples "may be considered as normal clinical practice" (6) and thus normally may form part of an NIS, depending on the burden that it may require to the participants. An NIS is legally distinguished from a clinical trial[3] and thus does not fall within Directive 2001/20/EC on the *Implementation of Good Clinical Practice in the Conduct of Clinical Trials on Medicinal Products for Human Use* (5). That boundary between a clinical trial

[2] The terms 'study' and 'trial' are interchangeable.

[3] Directive 2001/20/EC, which puts forth European Union regulation on good clinical practice of clinical trials, defines a clinical trial as "any investigation in human subjects intended to discover or verify the clinical, pharmacological and/or other pharmacodynamic effects of one or more investigational medicinal product(s), and/or to identify any adverse reactions to one or more investigational medicinal product(s) and/or to study absorption, distribution, metabolism and excretion of one or more investigational medicinal product(s) with the object of ascertaining its (their) safety and/or efficacy"(5). This directive distinguishes a clinical trial from an NIS as defined above, and thus the directive on clinical trials clearly states in Article 1.1 that NISs are excluded from the scope of the directive: "This Directive does not apply to non-interventional trials" (5). As such, at least legally, there is a distinction between a clinical trial and an NIS.

and an NIS when questionnaires, interviews, and blood samples are used may have grey areas which we cannot amply address here; nevertheless, keeping this grey area in mind would be useful in our discussion later in this chapter.

We can further classify an NIS as data only (either anonymized, coded, or identifiable), such as registry studies and non-experimental studies that do not include randomization but has actual subject enrolment. This article deals with the second type of NIS.

III. The question of necessity of informed consent in phase IV NIS

The problem of informed consent in an NIS begins with the fact that at least in Europe, "the regulatory governance of NIS still suffers from significant disharmony … with some countries implementing very specific and detailed legislation (e.g., Spain), while other have no legislation at all (e.g., Austria)" (7). There is also no ICH document specifically for NIS or generally for observational studies. Pharmacovigilance guidelines, such as Volume 9A (6) and the ICH *Pharmacovigilance Planning E2E* (8) document, partly guide NISs, although these are limited to NISs that are safety studies. The CIOMS *International Ethical Guidelines for Epidemiological Studies* (9), which states that informed consent is a requirement in epidemiological studies unless a waiver is justifiable in "exceptional" circumstances, is the closest international guideline that addresses informed consent in NIS. We shall go back to this point later.

This lack of unified legislation leads to "considerable room for inconsistencies in the approach to ethical review" in observational studies (10). The necessity of informed consent is frequently questioned because of the threat of selection bias (11,12). Lemaire, pointing out the need for European legislation "adapted to the different categories of clinical research" (13), reacted to an article by Ferrer, Artigas, Levy, et al. who said that in a particular quality improvement clinical research, "the need for informed consent was waived in view of the observational … nature of the study" (13). What is interesting about this quote is the relation made between not needing informed consent and the observational nature of research. In one prospective, open-label study meant to "assess the clinical performance of a foam dressing in the management of open wounds" (14), the authors stated, "No inclusion or exclusion criteria were provided, rendering the study exempt from institutional review board approval or informed consent restrictions according to European research requirements" (14). Thus, again, we have authors who equate the observational nature of the study, plus the lack of inclusion and exclusion criteria, as a reason for informed consent "restrictions" exemption. Thus the question, is informed consent necessary for NIS?

To address the question on the necessity of informed consent in NIS, we ought to look into the possible reasons stated in current literature why informed consent may not be necessary for NIS. We can categorize these reasons as follows: potential benefits to society; risk is minimal or none; and autonomy is not meaningfully infringed.

A. The potential benefit to society argument

The first argument that waiving consent in NIS would greatly benefit science and society is what is often available in literature, especially in studies that demonstrate selection bias resulting from the informed consent requirement in observational research (11,12,15). This argument springs from the aspiration for optimal efficiency as well as the assertion that increased scientific efficiency in research results in better health services, or in the specific case of phase IV drug research, better estimation of treatment effects in therapeutic use (11). As such, better health services and increased knowledge about a drug's effectiveness and safety would in fact benefit more and would, in the long run, reduce risk.

The main issue about this argument is that it does not touch on the very purpose of informed consent; instead, it goes straightaway into the 'benefits' of waiving it. Informed consent, as stated by Levine in the *Encyclopedia of Bioethics*, has a two-fold purpose: to minimize risk of research subjects, and to respect persons by giving them the right to choose (otherwise called the right to autonomy) (2). As such, without discounting the enormous value of phase IV drug research on therapeutic use, arguing for the waiving of informed consent solely because of this value misses the point. Simply, the argument fails due to irrelevance. It is one thing to have valid and efficient research, and it is quite another to respect the basic right of human beings to choose for themselves. Therefore, the potential benefit to society argument per se does not give us reasonable grounds to think that informed consent is not necessary.

B. Risk as minimal argument

This second argument states that informed consent is not necessary in NIS since its observational nature that utilizes "safe, evidence-based, and standard procedures" (16) does not impose additional risks or at most imposes only minimal risks and burdens to the study participants. The research may continue with virtually no involvement of the researcher in terms of prescription (if the researcher is distinct from the attending physician), and diagnostic and monitoring procedures are well within clinical practice. The question is, since NIS works within clinical practice and therefore no additional risks are imposed or at most research-related risks are minimal, is this sufficient argument to say that informed consent is not necessary?

This argument is closer to the one of the purposes of informed consent, i.e., the minimization of risk in studies. Nevertheless, it is one thing to say that informed consent protects research participants from risk, and it is quite another to say that the absence of risk justifies not asking for consent. Protection against unacceptable risk is an intended effect of informed consent by ensuring that the risks of a study are known and evaluated also by the prospective participant. Nevertheless, the fact that risks are minimal or even absent does not give the researcher the liberty or the right to include a person in a research without consent. If the right to choose, which is one of the purposes of informed consent, is a de facto basic right, then a person may exercise that right irrelevant of the external state of affairs, i.e., whether risk is present or not. Besides, wrongdoing is not restricted to physical harm, as Feinberg eloquently explains in *The Moral Limits of the Criminal Law*. A person can be wronged without being harmed, which Feinberg categorically calls "harmless wrongdoing" (17,18). As such, the risk as minimal argument per se is also an insufficient argument to justify the non-necessity of informed consent.

C. No meaningful infringement of autonomy argument

The third argument states that informed consent is not necessary in NIS because its absence does not "amount to any meaningful infringement of patients' autonomy" (16) since, by alluding to the reasonable-person standard, "there could be no reasonable or ethical grounds for any patient to object to being included in the study without his or her consent" (16). Thus, an NIS that has been judged by an ethics committee to be reasonable must by default also be consented to.

Just like any argument that utilizes the reasonable-person standard argument, this argument also "encounters conceptual, moral, and practical difficulties" (19). On the conceptual level, as Beauchamp and Childress said, the concept of a "reasonable person" has not been carefully defined (19). Logically, it encounters the problem of falsely equating presumed consent with actual informed consent, and in this case, the former is allowed to effectively replace the latter. This then denies the person her/his actual right to exercise consent. It is conceptually more worthwhile to make a distinction between a "consentable" study as judged by an ethics committee and the actual informed consent of a participant.

On the moral level, since the no meaningful infringement of autonomy argument makes the whole exercise of consent depend upon the researcher's (or ethics committee's) perspective of what is reasonable and ethical, the essential moral purpose of informed consent is defeated. Since it is the generic right[4] of an agent to

[4] Generic rights are rights of agents as agents, i.e. no agency is possible without the perfect fulfilment of such rights. "The generic conditions of agency consist of what vulnerable agents need,

make plans for herself/himself (21) and to do so according to her/his own definition of purpose and fulfillment, it is immediately a violation of her/his generic right as an agent to prejudge that in this instance there are no reasonable or ethical grounds for her/him to object to consent. Simply put, as a competent agent, a person chooses what is reasonable for her/him, and her/his consent depends on herself/himself and not on a prejudgment by anybody else. This applies either to the bloodletting in NIS, or even in any other research. Therefore, the no meaningful infringement of autonomy argument also does not justify the non-necessity of consent.

Hence, we could say that informed consent is a widely accepted right that human beings have when it comes to participation in research, including NIS, and none of the arguments above show that NIS is an exception to this universal rule. Considering NIS in general, there is no compelling substantive justification for such a general infringement because experience shows that NIS can and is administered with informed consent, and thus it would be unethical to infringe a participant's generic right to consent simply for the convenience of the researchers when it is quite possible to obtain it and there are no urgent and convincing reasons not to do so. Given thus, a more reasonable question would be, are there more compelling substantive reasons to infringe the right to consent in a particular research?

The waivability of informed consent in a particular research denotes the existence of "substantive justifications" (20) for the waiving. Take note that when consent is waived, this means that there is a prima facie right to consent (20) and this right is considered to be justifiably waivable based on the circumstances of a particular research. Thus, there are "exceptional" circumstances (9) when an NIS can be done without informed consent. The usual justification for the waiving of consent is the "impracticability" of it in certain types of studies (22), and even that justification must meet certain conditions[5]. If a considerable grey area exists in a study such that bloodletting has reached a point of being burdensome and thus a study that is technically an NIS is beginning to feel like a clinical trial to a participant, then it is highly doubtful that impracticality is sufficient reason to waive this right to consent.

Thus, although there may be particular instances when informed consent may be waived because of compelling substantive justificatory reasons, there are no ethically justifiable reasons to universally forego informed consent in NIS; in fact, there are prima facie ethical and legal reasons for it. Plainly, and in agreement with the CIOMS

irrespective of what their purposes might be, in order to be able to act at all or in order to be able to act with general chances of success" (20).

[5] Based on the American Common Rule, the conditions which all must be met are as follows: (a) the research involves no more than minimal risk; (b) the waiver or alteration will not adversely affect the rights and welfare of the subjects; (c) the research could not practicably be carried out without the waiver or alteration; and (d) whenever appropriate, the subjects will be provided with additional pertinent information after participation (22).

Ethical Guidelines for Epidemiological Studies (9), informed consent must be the standard in NIS, and waiving it must be an exception.

IV. On the application of informed consent in NIS

Saying that informed consent is a standard requirement in NIS is different from saying that the informed consent in NIS ought to be the same as the informed consent process that happens in phases I–III. That there is a difference in immediate goals, procedure, and scope between NIS and earlier trials tell us that this may also account for a different approach in informed consent. That differences in study procedure and norms may account for differences in informed consent application has been previously suggested by Burgess (23) and Hansson (24). Nevertheless, the question remains, "how can informed consent in phase IV be different from that of earlier phases?"

In the *Oxford Textbook of Clinical Research Ethics*, Flory, Wendler, and Emanuel (25) named four factors that are relevant for informed consent in health research, namely: understanding the purpose of research, understanding voluntariness, understanding protocol design and randomization, and understanding of risks and benefits. We shall go into these factors and see their relevance in NIS research.

First, when we speak of understanding the purpose of research, we refer to understanding the general information about the study, some specific information, the purpose of the study (which in other phases primarily refers to "creating generalizable knowledge" and benefiting future patients), and with it the avoidance of therapeutic misconception. All these are the universal concerns in earlier phases, and phase IV shares the concern of making sure that participants understand what the research is about and what if any does it ask from them (like answering questionnaires). But phase IV NIS differs from other phases since therapeutic misconception[6] ought not to be a concern since it is reasonable for participants to expect from the medical intervention which by now is considered as standard clinical practice. Also, since there ought to be virtually "no additional diagnostic or

[6] Therapeutic misconception (TM) "involves a research participant's failure to recognise how personal care (i.e., the obligation of physicians to make medical decisions solely with the patient's interest in mind) may be compromised by research procedures…this core concept of TM could be manifest in two ways: when participants express an incorrect belief that their individualised needs will determine assignment to treatment conditions or lead to modification of the treatment regimen (TM1); or when participants offer an unreasonable appraisal of the nature or likelihood of medical benefit from participation in the study, due to a misperception of the research enterprise (TM2)" (26).

monitoring procedures" (5) in NIS, then the risk of misperceiving research as clinical is almost nil.

Second, understanding voluntariness refers to the awareness of participants that they could withdraw without any consequence to their health care (25). This concern is something that phase IV NIS shares with the other phases since it is very possible that participants would consider participation in research as a requirement for their care.

Third, as regards understanding protocol design and randomization, the challenge in NIS is simpler compared to earlier phases since, though NIS researchers would need to make sure that participants understand that their information is important in research and that they would probably need to fill out some questionnaires or answer some interview questions, researchers need not struggle with explaining randomization, a concept that some researchers show is difficult for participants to understand (25).

Fourth, as regards understanding risks and benefits, earlier phases are concerned about too much optimism about the benefits of an investigational medicinal product, or confusion or lack of understanding about the benefits and risks of a trial drug. For NIS, this ought not to be a concern since the expectations as well as the understanding of risks and benefits of a marketed drug all fall into clinical practice and not into the study per se. This is what is meant by an NIS not having additional risks.

As such, informed consent concerns in phase IV NIS have substantial differences compared to the traditional informed consent concerns that mostly are applicable to earlier phases of a drug trial. But then again, how does this translate to the application of informed consent in phase IV NIS?

V. Manner and content of informed consent in NIS

Informed consent in phase IV NIS is different from that of earlier trials in the sense that ethical concerns may revolve around the very issue of the necessity or waivability of consent and that since research-related risks are very minimal if not non-existent, the relevant factors in the informed procedure are expectedly fewer. Thus the informed consent process may be different from the other phases in at least two aspects: the content of the informed consent form and the manner of the informed consent procedure. We have already seen above how the content of the informed consent form in NIS may be different from the informed consent form used in other phases, as an NIS, compared to that of other phases, is less demanding to participants when it comes to the four factors for informed consent in health research. Thus, an NIS informed consent form would need to contain information about the purpose of

the research, an explanation that research participation is voluntary, some information about the protocol, and some statements about risks and benefits, if any. But it need not address therapeutic misconception and randomization since these are irrelevant, and statements about benefits and risks cannot be as scrupulous as those in earlier phases as the trial per se should not carry more than minimal risk, and ideally should impose no additional risks.

Regarding the manner of the informed consent procedure, the regular opt-in procedure remains the ideal standard (9); nevertheless, there may be instances when a regular opt-in procedure is impracticable or may compromise the integrity of the research. In this case, an opt-out procedure may be considered preferable or more suitable. Some trials have demonstrated that an opt-out system could truly help in overcoming some of the problems on recruitment barriers (27), as well as the problem of selection bias threat, but our concern is, could an opt-out system truly "inform" a participant, or would this be an institutional informed consent that does not necessarily facilitate autonomous authorization (19)?

Looking at the defunct UK opt-out system where an initial information letter from the National Health Service gives the patients the chance to opt-out by not making their contact information available to research teams, Hewison and Haines found that many do not really object to this opt-out system (28). In fact, Hewison and Haines consider this system as more supportive of the aim to inform than the opt-in system since this opt-out system immediately puts the researcher in contact with the participant, thus providing the "support and reassurance that personal contact can provide" (28). Another study by Clark and Findlay (29) demonstrated how strategic information dissemination plus the ease of a system to opt-out addresses the worries of an opt-out system being deficient in terms of informing and allowing the participants to choose. As such, an opt-out system may be part of the different ways in which informed consent may be secured in a phase IV NIS, as long as it satisfactorily addresses the purposes of informed consent and the necessary factors relevant in the informed consent procedure.

VI. Conclusion

Informed consent in phase IV NIS is a necessary factor which may be waived in exceptional situations, as long as a valid substantive justification is in place. The distinct character of phase IV NIS also gives a different slant to the manner and content of informed consent such that not all the relevant factors for informed consent in health research are applicable to NIS, and both opt-in and opt-out procedures may also be utilized, as long as a person's participation in an NIS remains informed and voluntary.

Reference List

(1) International Conference on Harmonisation. General considerations for clinical trials E8. 1997.

(2) Levine RJ. Informed consent: Consent issues in human research. Encyclopedia of Bioethics. 3rd ed. 2004. p. 1280-90.

(3) Manson NC, O'Neill O. Rethinking informed consent in bioethics. Cambridge, New York: Cambridge University; 2007.

(4) The European Medicines Agency road map to 2015: the agency's contribution to science, medicine, health (draft for public consutation), 2010.

(5) European Parliament. Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. 2001.

(6) Eudralex Volume 9A. In: McCully S. Non-interventional studies. Compliance Healthcheck Consulting UK 2009.

(7) McCully S. Non-interventional studies. Compliance Healthcheck Consulting UK 2009.

(8) International Conference on Harmonisation. Pharmacovigilance planning E2E. 2004.

(9) Council for International Organizations of Medical Sciences. International ethical guidelines for epidemiological studies. 2008.

(10) Cuttini M, Saracci R. Commentary: Can we facilitate the ethical approval of international observational studies? Int J Epidemiol 2009 August;38(4):1108-9.

(11) Buckley B, Murphy AW, Byrne M, Glynn L. Selection bias resulting from the requirement for prior consent in observational research: a community cohort of people with ischaemic heart disease. Heart 2007 September;93(9):1116-20.

(12) Al-Shahi R, Vousden C, Warlow C. Bias from requiring explicit consent from all participants in observational research: prospective, population based study. BMJ 2005 October 22;331(7522):942.

(13) Lemaire F. Informed consent and studies of a quality improvement program. JAMA 2008 October 15;300(15):1762-3.

(14) Zoellner P, Kapp H, Smola H. A prospective, open-label study to assess the clinical performance of a foam dressing in the management of chronic wounds. Ostomy Wound Manage 2006 May;52(5):34-2.

(15) Tu JV, Willison DJ, Silver FL, Fang J, Richards JA, Laupacis A et al. Impracticability of informed consent in the Registry of the Canadian Stroke Network. N Engl J Med 2004 April 1;350(14):1414-21.

(16) Miller FG, Emanuel EJ. Quality-improvement research and informed consent. N Engl J Med 2008 February 21;358(8):765-7.

(17) Feinberg J. Harmless wrongdoing. New York: Oxford University; 1990.

(18) Feinberg J. Offense to others. New York: Oxford University; 1985.

(19) Beauchamp T, Childress J. Principles of biomedical ethics. 6th ed. New York: Oxford University; 2008.

(20) Beyleveld D, Brownsword R. Consent in the law. Oxford: Hart; 2007.

(21) Bielby P. Competence and vulnerability in biomedical research. Dordrecht: Springer; 2008.
(22) Capron AM. Legal and regulatory standards of informed consent in research. In: Emanuel E, Grady C, Crouch RA, Lie RA, Miller FG, Wendler D, editors. The Oxford textbook of clinical research ethics.New York: Oxford University; 2008. p. 613-32.
(23) Burgess MM. Proposing modesty for informed consent. Soc Sci Med 2007 December;65(11):2284-95.
(24) Hansson MO. Balancing the quality of consent. J Med Ethics 1998 June;24(3):182-7.
(25) Flory J, Wendler D, Emanuel E. Empirical issues in informed consent for research. In: Emanuel E, Grady C, Crouch RA, Lie RA, Miller FG, Wendler D, editors. The Oxford textbook of clinical research ethics.New York: Oxford University; 2008. p. 645-60.
(26) Appelbaum PS, Lidz CW, Grisso T. Therapeutic misconception in clinical research: frequency and risk factors. IRB 2004 March;26(2):1-8.
(27) Kavasery R, Maru DS, Sylla LN, Smith D, Altice FL. A prospective controlled trial of routine opt-out HIV testing in a men's jail. PLoS One 2009;4(11):e8056.
(28) Hewison J, Haines A. Overcoming barriers to recruitment in health research. BMJ 2006 August 5;333(7562):300-2.
(29) Clark AM, Findlay IN. Attaining adequate consent for the use of electronic patient records: an opt-out strategy to reconcile individuals' rights and public benefit. Public Health 2005 November;119(11):1003-10.

Chapter 3

IS INFORMED CONSENT NECESSARY FOR RANDOMIZED PHASE IV 'OBSERVATIONAL' DRUG STUDIES?

R. D. Bernabe, G. J. van Thiel, J. A. Raaijmakers, and J. J. van Delden. Is informed consent necessary for randomized Phase IV 'observational' drug studies? Drug Discov.Today 16 (17-18):751-754, 2011.

Abstract

This chapter addresses the question whether informed consent (IC) can be waived in Phase IV randomized observational drug studies (P4RODSs). To do this, it was first necessary to establish that the term P4RODS is a contradiction precisely because randomization necessarily makes a study "interventional," hence P4RIDS. Once this was established we argued that, based on the right and the harm principles, universally waiving IC in P4RIDS is ethically unjustifiable. Looking into public health and the nature of equipotent and bioequivalent drugs were also insufficient rationale to justify circumstantial waiving of IC. We conclude that IC can never be waived in P4RIDS, although an opt-out procedure in minimal risk studies could be ethically acceptable.

I. Introduction

There are Phase IV drug trials registered (http://clinicaltrials.gov/) that are categorized as being observational as well as randomized. Just like other randomized studies, such trials could be randomizing individuals or clusters (1), and randomizing these participants into two or more authorized drug or placebo groups (2). Nevertheless, these studies are categorized as observational because, apart from randomization, all other procedures are considered as 'standard clinical procedures'.

Because these drug studies are categorized as observational, and in exceptional circumstances informed consent (IC) can be waived in observational studies (3), the question of whether IC could also be conditionally waived in these studies arises. Hence, we shall deal with the question: is it ever justifiable for a Phase IV randomized observational drug study (P4RODS) not to have IC? We shall restrict ourselves to P4RODS that are concerned with continuous and postauthorization drug development, and exclude quality assessment and/or quality improvement studies that are meant to monitor and evaluate systematically "the various aspects of a project, service or facility to ensure that standards of quality are met" (4).

As we shall see below, this kind of study has been going on and is in no way an exceptional case. In fact, our question is something that is tackled occasionally by individual ethics committees; nevertheless, we do not know of any systematic ethical evaluation of P4RODS in the medical research ethics literature. Thus, there is a real need to explore and discuss the ethical issues in P4RODS, a task we hope to begin by looking at IC and P4RODS.

II. Conceptual difficulty of P4RODS

P4RODS is a drug study carried out after drug approval and in connection with the approved indication of the drug (5) wherein the study participants, all of whom are patients, receive standard clinical care. At the same time, they are randomized individually or as a cluster to a specific drug or placebo (2). Clinicaltrial.gov provides us with several examples-some of which include the evaluation of two antibiotic regimens on pediatric perforated appendicitis patients (6) and the cluster study of two approaches for tuberculosis control in Brazil (1), among others.

The conceptual difficulty with P4RODS stems from the combination of the terms 'randomized' and 'observational'. The problem arises because the US National Institute of Health (NIH) and the European Commission (EC) have differing definitions of an observational study. NIH defines an observational study as:

> A biomedical or behavioral research study of human subjects designed to assess risk factors for disease development or progression, assess natural history of risk factors or disease, identify variations based on

> geographic or personal characteristics (such as race and/or ethnicity or gender), track temporal trends, or describe patterns of clinical care and treatment in absence of specific study-mandated interventions (7).

The EC, using the term noninterventional study to refer to an observational study, defines an observational study as:

> A study where the medicinal product(s) is (are) prescribed in the usual manner in accordance with the terms of the marketing authorization. The assignment of a patient to a particular therapeutic strategy is not decided in advance by a trial protocol but falls within current practice and the prescription of the medicine is clearly separated from the decision to include the patient in the study. No additional diagnostic or monitoring procedures shall be applied to the patients, and epidemiological methods shall be used for the analysis of collected data (8).

US and EU regulations state that an observational study is characterized by its noninterventional nature where the study protocol does not affect standard clinical practice and, thus, the absence of "specific study-mandated interventions." Nevertheless, EU regulation is more straightforward, concrete and subsuming in its definition of what an observational study is: an observational study cannot be such that: (i) therapy is dictated by the protocol; (ii) medical prescription has something to do with the participant's inclusion in a study; and (iii) additional diagnostic or monitoring procedures are applied to the participants. If we consider the nature of P4RODS and the fact that it involves randomization, which means that treatment is done "by chance" according to some random allocation (9), and in some instances even placebo is involved, then such a study would necessarily fall into categories (i)–(iii). These are the very factors that define what an observational study is not. As such, conceptually, P4RODS is a contradiction.

If we are to resolve this contradiction, there are two ways: first, we could propose to change the definitions of the regulations; and, second, we could propose to reclassify P4RODS. Redefining regulations to accommodate randomization (and thus accommodate (i)–(iii), see above) within the very definition of an observational study would result in blurring the substantial difference between interventional and observational studies. This obviously would not make sense. The next option would be to reclassify P4RODS.

Reclassification of such studies, such that P4RODS would be categorized as interventional instead of observational, would help greatly toward fruitful and open discussions on these studies. It is difficult to understand why P4RODS was allowed to

be classified as observational when reading the regulations would point in the opposite direction. It is important to note that the intensity of intervention does not change the nature of the trial. An interventional trial will remain as such, even if it is just a matter of randomizing a wound patch for example, as long as neither the doctor nor the patient had the chance to make their preferences have any bearing on the therapy provided. Thus, an intervention of some sort was present in what should have just been a plain patient–doctor relationship in standard clinical practice.

If we wish to discuss IC in terms of this type of study, we ought to make the mindset shift and conclude that this study is in fact interventional. This way, we shall direct our discussion toward evaluating the waiving of IC in interventional studies that are randomized only in terms of the therapy provided, and not in terms of the overall procedure. The next steps would involve discussing the possibility of a justified waiver of IC in a Phase IV randomized interventional drug study (P4RIDS).

III. Universal waiving of IC in P4RIDS

In the previous chapter, we have argued that the commonly presented reasons for the universal waiving of IC in noninterventional studies involving patient enrollment cannot be accepted as justifiable rationale per se (10). Arguments that involve potential benefit to society, risk as minimal or no meaningful infringement of autonomy are insufficient arguments for the universal waiving of IC in such studies because these arguments do not even touch on the meaning and purpose of IC, which is “not only to minimize risk but also to give persons the right to choose” (11). Any argument for the universal waiving of IC in noninterventional studies involving actual patient enrollment (as opposed to data-only studies) must state why respecting the individual's right to choose and minimizing risks are always less important concerns in such studies. Such an argument does not exist. The individual's right to choose, or better yet the right to be autonomous, is a basic generic right. Generic rights refer to rights that are also preconditions for any human action (12), without which the agency of a person is denied. Hence, if these reasons are insufficient to justify the waiving of IC in noninterventional studies, we could expect that they are insufficient too for interventional studies such as P4RIDS.

Closely in connection with the IC as a generic right argument is the argument that waiving of IC in studies such as P4RIDS is harmful or maleficent. By harm we refer to the wrongful hindrance of another's interest (13). Analytically, Feinberg breaks down this definition of harm as follows:

> (i) A acts (ii) in a manner that is defective or faulty in respect to the risks it creates to B. That is, with the intention of producing the consequences for B

> that follow, or similarly adverse ones, or with negligence or recklessness in respect to those consequences; (iii) A's acting in that manner is morally indefensible, that is, neither excusable nor justifiable; and (iv) A's action is the cause of a setback to B's interest, which is also (v) a violation of B's right (13).

A universal waiving of IC in P4RIDS could be considered an act (and thus (i)) that risks the participants' exercise of self-determination, trust and/or health with full-intent or recklessness (and thus (ii)). Such a universal waiving of IC in P4RIDS cannot be excused or justified because that would also mean universally risking the participants' self-determination (or autonomy), trust and/or health (and thus (iii)). Such a universal waiving is definitely a setback to the participants' interest and, in this case, welfare interests are impeded. Welfare interests are those "minimal interests" that are "basic requisites of a man's well-being" (13) such that damaging one would affect a person's network of interests. Self-determination, trust and health obviously fall within this category. As such, and because welfare interests are "the grounds for valid claims against others par excellence" (13), the universal waiving of IC in P4RIDS is in fact a grave setback of interest (and thus (iv)), which, as earlier stated, is also a violation of the participants' generic rights (and thus (v)). As such, in terms of rights and harms, a universal waiving of IC is not ethically justifiable.

Nevertheless, we have also previously argued that the waiving of IC in noninterventional studies can be circumstantially justified as long as a substantive justification and an acknowledgement of the waiving of rights are in place (10). An example of such a justification is the impracticability argument in noninterventional studies of high importance. Thus, the possibility of a substantive justification for the circumstantial waiving of IC in P4RIDS is what we would have to look at next.

IV. Circumstantial waiving of IC in P4RIDS

Manson and O'Neill argue that IC is not necessary for all medical interventions (14). When it comes to public health goods, variations in individual choices cannot be accommodated (14) and, hence, compulsion might be defensible for such goods (15). The basic question then would be: could we consider certain or all of P4RIDS as public health goods? By public health, we refer to "the collective action by a community or society to protect and promote the health and welfare of its members" (16). It is a communal effort to prevent disease and premature death (17), most of the time led by the government, but with the involvement of "nongovernmental and quasi-public institutions" (17) as well. Given this definition, it would be difficult to classify most nongovernmentally backed P4RIDS as public health goods and, thus, the discussion on the waiving of IC in most P4RIDS cannot happen within the public health arena.

Simply put, the fact that IC in P4RIDS can be waived because of public health reasons cannot be considered a substantive justification for most P4RIDS.

Though public health may not be an avenue to search for potential justifications, the very characteristics of the drugs may be. First, there are drugs that might be considered as equipotent. Equipotence refers to the "equivalence of the two medications in terms of either the concentration or amount needed to produce a defined effect" (18). Thus, for example, 400 mg of celecoxib and 150 mg of diclofenac per day for rheumatoid arthritis are said to be equipotent (19). Nevertheless, two equipotent drugs do not necessarily have the same toxicity profiles: celecoxib and diclofenac "gave significantly different incidences of ulcer" (19). Hence, a rheumatoid arthritis patient who is predisposed to ulcers should clinically receive the indication that results in lower incidences of ulcer. Second, two tested drugs can be considered as bioequivalent. That is, "… their bioavailabilities (rate and extent) after administration in the same molar dose lie within acceptable predefined limits. These limits are set to ensure comparable in vivo performance, i.e., similarity in terms of safety and efficacy" (20).

When two medicinal products are bioequivalent, such as a generic drug and a reference medicinal product, or an approved modified released product and its original immediate release form, then, for all intents and purposes, they are considered similar both in safety and efficacy. Thus, a P4RIDS on bioequivalent medicinal products that utilizes approved dosages is ideally not adding substantial research-related risks to the participants. Nevertheless, we also know that a bioequivalence study that looks into the extent and rate of a drug's availability (21, 22) would definitely have not only research relevance but clinical relevance as well. If two bioequivalent drugs were exactly the same there would be no point in randomizing them in a Phase IV drug development study. The potential or expected difference between the two drugs spells out the risks that must be accounted for and stated in the IC form.

There could be situations where risks are minimal or inconveniences instead of risks are prominent, such as in bioequivalent studies of modified release products. It must be made clear that inconvenience has been traditionally placed within the benefit-risk ratio (23) such that a benefit-risk assessment always takes into account the added inconvenience that a trial brings (24). Hence, the inconvenience of taking a drug four times a day is definitely clinically relevant compared with the convenience of taking a drug once a day. This inconvenience can be escalated to the level of physical risk in special populations – for example when geriatric patients are involved. Hence, in cases of P4RIDS on medicinal products that are equipotent or bioequivalent, physicians are restricted from choosing "what they think is best." Also, in studies that involve equipotent drugs the added risk of variable toxicity is present. Even in the

absence of grave risks such as in P4RIDS on bioequivalent drugs, there might still be potential clinically relevant differences between the two drugs, and inconveniences could be expected especially in studies including modified release products.

The issue of conflict of interest is another point that must not be neglected, even in P4RIDS that are bioequivalence studies involving minimal risks. Patients' trust and circumstances are used when other factors unknown to them that relate to the physician–researcher's or the institution's immediate gain come into the picture in matters of decisions on prescription. Conflict of interest, at either the investigator–physician or the institutional level, is something that patients have the right to know about, especially the known compromises that come with their prescribed therapy. The deviation from the usual decision-making process of a physician must be accounted for because it would affect the "usual" situation that patients are familiar with. This change from what used to be the status quo must be made in agreement with the patients if research and medical practice are to retain (or gain) the patients' trust (25). As such, neither bioequivalence nor equipotence is a sufficient substantive justification for the circumstantial waiving of IC or, at the very least, for the right to be informed and to make decisions based on such information.

Thus, IC ought to remain the standard in P4RIDS, although we are of the position that concerns such as bias and recruitment barriers in P4RIDS with minimal risks could warrant an opt-out consent procedure. An opt-out procedure enrolls participants by default, as opposed to an opt-in IC procedure that recruits participants, explains the procedures and secures their signed IC forms. The participants in an opt-out procedure shall be informed through various possible media of their inclusion in a study and their right to withdraw at any time without consequence. There have been studies on opt-out procedures that effectively inform and allow the patient to choose (26, 27). These procedures can essentially alleviate concerns of violating generic rights. Without the troubles of an institutional IC (28), but still taking care that patients are properly and effectively informed of the trial and their right to opt-out, such a system could help address the practical problems that can come with IC in P4RIDS with minimal risks.

V. Concluding remarks

P4RODS is a conceptual contradiction. Instead of wrongly categorizing such a study it would be best to acknowledge its interventional nature, and thus P4RIDS. The universal waiving of IC is not ethically justifiable because it would violate generic rights and is maleficent. Regarding the circumstantial waiving of IC, the argument for public health as a justification for this sort of waiving arose; but it was not the proper locus to research when looking for substantive justifications for the waiving of IC.

Equipotence and bioequivalence were also investigated, and both were insufficient grounds to waive the process of informing patients and respecting their choices. As such, consent remains a moral necessity and the total waiving of consent, either universally or circumstantially, is ethically unjustifiable. IC remains the standard, although an opt-out procedure might be warranted for low risk P4RIDS.

Reference List

(1) Johns Hopkins University. Innovative approaches to tuberculosis control. National Library of Medicine (US) 2009;Available from: URL: ClinicalTrials.gov.

(2) Wyeth. Effect of Bazedoxifene, Raloxifene, and placebo on breast densitiy. National Library of Medicine (US) 2010;Available from: URL: ClinicalTrials.gov.

(3) Council for International Organizations of Medical Sciences. International ethical guidelines for epidemiological studies, 2008.

(4) Merriam-Webster. “Quality assurance”. Merriam-Webster Dictionary, 2011.

(5) International Conference on Harmonisation. General considerations for clinical trials E8, 2010.

(6) Children's Mercy Hospital Kansas City. Prospective randomized evaluation of antibiotic regimen following appendectomy for perforated appendicitis. National Library of Medicine (US) 2007.

(7) Department of Health and Human Services (US), National Heart LaBIU, National Institute of Health (US). Is my study observational or interventional? National Heart, Lung, and Blood Institute (US) 2010.

(8) European Parliament. Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. 2001.

(9) Glasser SP. Clinical trials. In: Glasser SP, editor. Essentials of clinical research. Springer; 2008. p. 29-62.

(10) Bernabe R, van Thiel G, Raaijmakers J, van Delden J. Informed consent and phase IV non-interventional drug research. Current Medical Research & Opinion 2011;27(3):513-8.

(11) Levine RJ. Informed consent: consent issues in human research. Encyclopedia of Bioethics, 3rd ed. 2004.

(12) Gewirth A. Human rights and conceptions of the self. Philosophia 1988;18(2-3):129-49.

(13) Feinberg J. Harm to others. Oxford, New York: Oxford University Press; 1984.

(14) Manson NC, O'Neill O. Rethinking informed consent in bioethics. Cambridge, New York: Cambridge University; 2007.

(15) O'Neill O. Informed consent and public health. Philosophical Transactions of the Royal Society of London 2004;359:1133-6.

(16) Duffy J. Public health: history. Encyclopedia of Bioethics, 3rd. 2004. p. 2206-10.

(17) Beauchamp DE. Public health: philosophy. Encyclopedia of Bioethics, 3rd. 2004. p. 2210-4.

(18) Curry S, McCarthy D, DeCory H, Marler M, Gabrielsson J. Phase I: the first opportunity for extrapolation from animal data to human exposure. In: Edwards L, Fletcher A, Fox A, Stonier P, editors. Principles and practice of pharmaceutical medicine. 2nd ed. West Sussex: Wiley; 2007. p. 79-100.

(19) Furst DE. Pharmacology and efficacy of cyclooxygenase (COX) inhibitors. Am J Med 1999 December 13;107(6A):18S-22S.

(20) Committee for Medicinal Products for Human Use. Guideline on the investigation of bioequivalence, draft. 2009. 10-12-2010.

(21) Gad, SC. (Ed.), Drug safety evaluation. Wiley; 2002.

(22) Pfizer. Bioequivalence study comparing a new 80 mg atorvastatin tablet to a 80 mg atorvastatin commercial ablet. National Library of Medicine (US) 2009;Available from: URL: ClinicalTrials.gov.

(23) Levine, R.J. (Ed.). Ethics and regulation of clinical research. Urban & Schwarzenberg ; 1981.

(24) Van Luijn HE, Aaronson NK, Keus RB, Musschenga AW. The evaluation of the risks and benefits of phase II cancer clinical trials by institutional review board (IRB) members: a case study. J Med Ethics 2006;32 (3):170-176.

(25) Tenery Jr. RM. Is informed consent always necessary for randomized controlled trials? N Engl J Med 1999;341(6):450.

(26) Hewison J, Haines A. Overcoming barriers to recruitment in health research. BMJ 2006 August 5;333(7562):300-2.

(27) Clark AM, Findlay IN. Attaining adequate consent for the use of electronic patient records: an opt-out strategy to reconcile individuals' rights and public benefit. Public Health 2005 November;119(11):1003-10.

(28) Beauchamp T, Childress J. Principles of biomedical ethics. 6th ed. New York: Oxford University; 2008.

Chapter 4

CONSENT IN PSYCHIATRIC BIOBANKS FOR PHARMACOGENETIC RESEARCH

R.D. Bernabe, F. H. van der Baan*, A. L. Bredenoord, J. G. Gregoor, G. Meynen, M. J. Knol, and G. J. van Thiel. Consent in psychiatric biobanks for pharmacogenetic research. Int.J.Neuropsychopharmacol. :1-6, 2012.*

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Abstract

In psychiatric practice, pharmacogenetics has the potential to identify patients with an increased risk of unsatisfactory drug responses. Genotype-guided treatment adjustments may increase benefits and reduce harm in these patients; however, pharmacogenetic testing is not (yet) common practice and more pharmacogenetic research in psychiatric patients is warranted. An important precondition for this type of research is the establishment of biobanks. In this paper, we argue that, for the storage of samples in psychiatric biobanks, waiving of consent is not ethically justifiable since the risks cannot be considered minimal and the argument of impracticability does not apply. An opt-out consent procedure is also not justifiable, since it presumes competence while the decisional competence of psychiatric patients needs to be carefully evaluated. We state that an enhanced opt-in consent procedure is ethically necessary, i.e. a procedure that supports the patients' decision-making at the time when the patient is most competent. Nevertheless, such a procedure is not the traditional exhaustive informed consent procedure, since this is not feasible in the case of biobanking.

I. Case

A 40-year-old woman, exhibiting psychotic symptoms, with no previous history of psychiatric illness, is acutely admitted to a psychiatric clinic. As part of routine care, blood is drawn to assess her somatic condition. Antipsychotic treatment, which is started immediately, consists of 2 mg haloperidol daily. The patient's blood sample is used to predict her drug metabolizing capacity by genotyping cytochrome P450 2D6. This enzyme is involved in the metabolism of many antipsychotics. The pharmacogenetic test results show that this patient has an increased metabolic activity and is therefore at risk for low serum levels and decreased activity of haloperidol when given the standard dose. However, guidelines on dose adjustment are currently lacking for this genotype (1).

In psychiatric practice, predicting a patient's response to a specific drug is difficult, which complicates finding the optimal drug and dose for a patient. Pharmacogenetic testing is not (yet) common practice in psychiatry and more pharmacogenetic research in psychiatric patients is warranted to determine the clinical implications of genotype-guided treatment (2). In our case, the patient's blood was collected for clinical purposes. Future (pharmacogenetic) research could be facilitated by storage and use of blood samples. This raises the question of whether, and under what conditions, researchers are allowed to store and use such samples for research. Is consent required? The issue of consent is particularly a challenge here since the samples are not collected in a trial setting where informed consent is standard for participants. Also, if consent is required, is use of the sample allowed if the patient is not competent at the moment of blood withdrawal?

This paper identifies and explores what type of consent is appropriate in psychiatric biobanks that are built and maintained primarily for pharmacogenetic research purposes and the consequences for patients and psychiatric health professionals. Specifically, this paper focuses on psychiatric patients admitted in the acute ward. This patient population is not as extensively studied as the others, which results in little evidence on (personalized) treatment. Blood withdrawal is part of routine care of these patients and, at least in some psychiatric hospitals in the Netherlands, pharmacogenetic testing is already routinely done, as illustrated in the case. We hope to contribute to the future organization of psychiatric hospitals, in which samples are stored and research is enabled in an ethically justifiable way.

II. Biobanks

The overall rationale of biobanks is to house and facilitate ongoing research on human biological material (3). They vary according to the type and number of tissues stored, the extent of genetic, clinical and personal data and the permitted use of the

samples and data. In large databases such as the UK Biobank, samples are usually specifically collected for research aims. In smaller hospital-based, disease-specific (or clinical) biobanks, samples are collected and stored for diagnosis and treatment, but any residual material can also be used for research. The introductory case is an example of such a biobank.

Biobank research has several special characteristics: samples are usually stored for a long time and biological samples can be matched with phenotypic data. The exact research questions for which the samples will be used are not formulated at the time of sample collection. This implies that being a donor for a biobank can have a greater impact than a donor may foresee. That underscores the importance of considering the appropriate type of consent, even more for the enrolment of potentially vulnerable groups. There has been debate on who should be considered "vulnerable" in research and for what reason (4). Nonetheless, the potential diminished capacity to consent and the context of being institutionalized are generally considered as inferring a need for special protection in medical research.

In the case of the 40-year-old woman, both factors apply.

III. Consent

Whereas consent is a standard ethical and legal requirement for clinical research, the appropriate type of consent for residual tissue and biobanking research is less consensual. Positions defended in the literature range from informed consent to a one-time general (or broad) consent to opt-out procedures to no consent at all (3;5-8). In addition, neither the type of consent nor the appropriate type of ethics review is a settled issue. After all, the debate on whether such types of research need approval of a research ethics committee (institutional review board) has recently been re-opened by a proposal by Emanuel & Menikoff (5) to exempt minimal risk research from ethics review. However, whether biobank research should automatically be allocated to the category of "minimal risk research" remains to be seen.

Table 1 gives an overview of the different forms of consent. In exceptional circumstances, consent is waivable (9;10). In addition to a substantive justification, two conditions are – according to international guidelines for storing human biological samples for future epidemiological research – necessary for waived consent: the risks to participants should be no more than minimal and obtaining consent would make the conduct of the research impracticable (9;11). Do these conditions apply to the woman in the case or to any in-patient in a psychiatric ward whose blood sample and DNA information are stored in a biobank with a pharmacogenetic research aim?

Forms of Consent			Information for Donor	Consequences for Research
Waived consent			Donor is not made aware that tissue may be used for research.	Substantive justification is necessary; subsequently, the sample can be used for research.
Consent	Opt-out		Through the use of various media for information dissemination, it is presumed that donor is aware that tissue may be used for research. If he/she does not explicitly decline consent, consent is granted. Competency of potential donor is presumed.	As long as consent is not explicitly declined, the sample can be used for research.
	Opt-in (informed consent)	Broad	Donor is actively informed that tissue may be used for research, although exact research questions are not specified. He/she has the option to agree or disagree with the collection and use of the tissue.	If consent to unspecified use of the sample is given (consent to governance), the sample can be used for research. When new research questions arise, the sample may be reused without renewed consent, as long as it falls within the scope of the broad consent.
		Specific	Donor is actively informed that tissue may be used for research and about the exact nature of the research and the research questions. He/she has the option to agree or disagree with the collection and use of the tissue.	If consent for specific research is given, the sample can be used for the specific research question. When new research questions arise, the donor must be approached to re-ask consent.

Table 1: Overview of different forms of consent with the consequences for donor and research

A. Minimal risk

Risk is considered minimal when the probability and magnitude of harm or discomfort anticipated in the research are not greater than those ordinarily encountered in daily life or during the performance of routine physical or psychological tests (12). Some have argued that the risks of biobank research are low or even non-existent (e.g., Petrini (13)), which indeed seems the case if researchers only have access to coded data and no individual results will be communicated to the patients or third parties. However, even in coded data, although the probability is small, the risk of revealing information must be considered since magnitude wise, as will be shown shortly, the risks could be noteworthy.

Even if physical risks may be negligible or even non-existent, this is not necessarily the case for other risks posed by a biobank, such as social, psychological and economical risks. The risks of biobanking research are largely informational, as they could encompass harm that results from the inappropriate release and distribution of information and not from the research intervention itself (5). The information stemming from (pharmaco-) genetic research may have beneficial consequences, but it can also cause distress and anxiety, affect someone's opportunity to maintain insurance or be stigmatizing (14-16). The amount and nature of information about a person is potentially limitless, which, if inappropriately disclosed, may affect the rights and well-being of the person in question, as well as his/her family's (14). As more people get to have access to such data from the psychiatric biobank, the risk of breaches in confidentiality also increases.

Such risk is not comparable to daily life risk nor to the risk of a routine (psychiatric) test. We do concede that risks may possibly be diminished to no more than minimal, given consensual safeguards within the biobanking system. This sets high demands on adequate systems of data security, feedback policy and risk management and clear guidelines regarding the use of tissues and data. It also requires awareness of biobank researchers regarding governance policies and, obviously, their compliance to these. The current status, particularly where infrastructures are built that makes it possible to link and network biobanks around the world in unprecedented ways (17), and the potential significance of genetic research results do not allow us to claim that the risks are minimal in nature.

B. Impracticability

In general, impracticability could be an issue if, for example, locating patients whose records will be used for research is difficult. For patients such as in our case, who are accessible at the moment of blood withdrawal, there is no obstacle to ask for consent for biobanking the sample – except when the patient is incompetent (see below).

Both conditions under which waiving of consent might be justified are not applicable in our case, thus waiving of consent is unethical here.

IV. Vulnerability and competence of psychiatric patients

Psychiatric patients admitted in the acute ward are considered to be 'cognitively vulnerable', although their degree of vulnerability varies over time (18). Their vulnerability partly depends on their decisional competence, i.e., the patient's capacity to decide given a specific situation (19) and, in our case, it is the capacity to decide to consent (or not) to biobank research.

It has been demonstrated that 'mental incapacity to make decisions on treatment is common in people admitted to psychiatric wards' (20). Although most studies deal with the capacity of psychiatric patients regarding treatment decisions, it seems reasonable that these findings are also applicable to decisional competence required for biobanking and research. The decisional competence of psychiatric patients fluctuates; patients are likely to regain competence when the acute phase of disease has passed and competency could again be jeopardized when symptoms recur. For some of these patients, supporting measures in a decision-making process are effective (21), so that otherwise incompetent psychiatric patients achieve sufficient decision-making capacity to consent. Other patients permanently lack decisional capacity, in which case a legal representative is necessary.

V. Type of consent

There are two possibilities for obtaining consent: an opt-in system and an opt-out system. The former entails explaining and making a patient sign an informed consent form; the latter involves making a patient know, either verbally or through a leaflet, about biobanking and about the opportunity to refuse it (9). Considering that an opt-out procedure is usually administratively easier, does it sufficiently protect the patient's rights and interests in our case?

The foregoing discussion points to the need to carefully evaluate the decisional competence of the patient to consent to biobanking and research. This requirement is contrary to the essence of an opt-out procedure, in which competency is presumed. Participants are assumed to have the competence to understand the research and to opt out, without confirming whether or not these capacities are indeed within the participants' competence. Moreover, although a positive normative judgment about the biobank research enterprise is probably rightly positioned as the default position, this can at the same time be subtly coercive for people who wish to deviate. Hence, an opt-out procedure is not ethically defensible in our specific case. Moreover, the assessment of competency approximates the very demands of an opt-in procedure,

save for the final signing of the informed consent form. An enhanced opt-in procedure that supports the patients' decision-making and promotes asking consent at the time when the patient is most competent is what is ethically necessary. The extra guidance can be in the form of technological aids, such as a videotape or PowerPoint presentation explaining the research procedures, although the human element seems pivotal (18). To illustrate, Lapid et al. (22) showed that a 30-min session with a psychiatrist discussing frequently raised concerns about a procedure increased understanding, reasoning and choice in elderly depressed persons. When a patient, despite the extra support, does not achieve sufficient decisional capacity during the admission, a legal representative should be allowed to give proxy consent. This type of consent will have administrative and procedural repercussions. Psychiatric health facilities that also biobank their patients' samples need to ensure that a supported informed consent procedure is in place. This means not only that forms and various media are available, but also that the health practitioners are briefed and trained to administer such a supportive informed consent process.

It is necessary to note that our endorsement of an opt-in procedure does not imply a traditional exhaustive informed consent procedure. Given the nature of biobanks, such a procedure is plainly not feasible because the traditional informational requirements (19;23) of an informed consent procedure are not available at the time of biobanking. There have been discussions about broad informed consent, which is consent on the unspecified use of samples for any type of biomedical study. We think that informed consent in psychiatric biobanks ought to be included within these discussions. An opt-in system, specifically for biobanking psychiatric patients' samples, should be developed to meet the ethical requirements of good research.

VI. Conclusion

In psychiatric biobanks where biomaterials with explicit DNA information are stored for pharmacogenetic research purposes, waiving of consent is not ethically justifiable since the risks of such biobanks cannot be considered minimal and the argument of impracticability does not apply. Neither is an opt-out consent procedure justifiable since it presumes competence and the decisional competence of a cognitively vulnerable group of psychiatric patients needs to be carefully evaluated. Only a supported opt-in procedure is justifiable in this case, that is, a procedure that considers the individual patient's condition and the time when the patient is most competent. As such, psychiatric health facilities that biobank need to ensure that they and their personnel are administratively and procedurally prepared for such consent.

Reference List

(1) Swen JJ, Nijenhuis M, de BA, Grandia L, Maitland-van der Zee AH, Mulder H et al. Pharmacogenetics: from bench to byte--an update of guidelines. Clin Pharmacol Ther 2011 May;89(5):662-73.

(2) Kirchheiner J, Seeringer A, Viviani R. Pharmacogenetics in psychiatry--a useful clinical tool or wishful thinking for the future? Curr Pharm Des 2010;16(2):136-44.

(3) Sheehan M. Can Broad Consent be Informed Consent? Public Health Ethics 2011 November;4(3):226-35.

(4) Levine C, Faden R, Grady C, Hammerschmidt D, Eckenwiler L, Sugarman J. The limitations of "vulnerability" as a protection for human research participants. Am J Bioeth 2004;4(3):44-9.

(5) Emanuel EJ, Menikoff J. Reforming the regulations governing research with human subjects. N Engl J Med 2011 September 22;365(12):1145-50.

(6) Helgesson G, Dillner J, Carlson J, Bartram CR, Hansson MG. Ethical framework for previously collected biobank samples. Nat Biotechnol 2007 September;25(9):973-6.

(7) Hofmann BM. Bypassing consent for research on biological material. Nat Biotechnol 2008 September;26(9):979-80.

(8) Wendler D. One-time general consent for research on biological samples. BMJ 2006 March 4;332(7540):544-7.

(9) International ethical guidelines for epidemiological studies, Council for International Organizations of Medical Sciences, 2008.

(10) US Department of Health ad Human Services. Federal policy for the protection of human subjects. 1991.
Ref Type: Statute

(11) Bernabe R, van Thiel G, Raaijmakers J, van Delden J. Informed consent and phase IV non-interventional drug research. Current Medical Research & Opinion 2011;27(3):513-8.

(12) Committee on Human Studies. Definitions. Harvard University Faculty of Medicine 2011 January 10;Available from: URL: http://www.hms.harvard.edu/orsp/human/IRBDefinitions.htm

(13) Petrini C. "Broad" consent, exceptions to consent and the question of using biological samples for research purposes different from the initial collection purpose. Soc Sci Med 2010 January;70(2):217-20.

(14) Bredenoord AL, Kroes HY, Cuppen E, Parker M, van Delden JJ. Disclosure of individual genetic data to research participants: the debate reconsidered. Trends Genet 2011 February;27(2):41-7.

(15) Haga SB, Burke W. Pharmacogenetic testing: not as simple as it seems. Genet Med 2008 June;10(6):391-5.

(16) Netzer C, Biller-Andorno N. Pharmacogenetic testing, informed consent and the problem of secondary information. Bioethics 2004 August;18(4):344-60.

(17) Kaye J. From single biobanks to international networks: developing e-governance. Hum Genet 2011 September;130(3):377-82.

(18) Bielby P. Competence and vulnerability in biomedical research. Dordrecht: Springer; 2008.

(19) Beauchamp T, Childress J. Principles of biomedical ethics. 6th ed. New York: Oxford University; 2008.

(20) Owen GS, Richardson G, David AS, Szmukler G, Hayward P, Hotopf M. Mental capacity to make decisions on treatment in people admitted to psychiatric hospitals: cross sectional study. BMJ 2008;337:a448.

(21) Dunn LB, Lindamer LA, Palmer BW, Schneiderman LJ, Jeste DV. Enhancing comprehension of consent for research in older patients with psychosis: a randomized study of a novel consent procedure. Am J Psychiatry 2001 November;158(11):1911-3.
(22) Lapid MI, Rummans TA, Pankratz VS, Appelbaum PS. Decisional capacity of depressed elderly to consent to electroconvulsive therapy. J Geriatr Psychiatry Neurol 2004 March;17(1):42-6.
(23) World Medical Asociation. Declaration of Helsinki: Ethical principles for medical research involving human subjects. 2008.

PART II:

WEIGHING OF BENEFITS AND RISKS

Chapter 5

THE NEED TO EXPLICATE THE ETHICAL EVALUATION TOOLS TO AVOID ETHICAL INFLATION

R. D. Bernabe, G. J. van Thiel, J. A. Raaijmakers, and J. J. van Delden. The need to explicate the ethical evaluation tools to avoid ethical inflation. Am.J.Bioeth. 9 (11):56-58, 2009.

Abstract

As a reaction to the article of Burris and Davis entitled, “Assessing social risks prior to commencement of a clinical trial: Due diligence or ethical inflation,” this commentary argues that the predicament they present regarding the use of the rapid policy assessment (RPA) social risk assessment method is an artificial predicament. Further, we argue that their “predicament,” and also therefore ethical inflation, can be avoided if we look at the issue not simply as an issue of “inflation” but an issue of clarity and transparency of what risk–benefit assessment is, and what tools may be needed to make this evaluation.

In the article, “Assessing social risks prior to commencement of a clinical trial: Due diligence or ethical inflation,” the authors spoke of the merits of the rapid policy assessment (RPA) social risk assessment method, but were also wary about unintentionally contributing to the increasing procedural burdens of researchers in the name of ethics, the so-called “ethical inflation” (1). As such, the authors do not endorse the standardization of empirical risk assessment by institutional review boards (IRBs), at least tentatively, since they also said that they are “unsure” if the risk assessment they did ought to be routine or not.

The wavering that is present throughout the article is reflective of the predicament in ethically assessing medical research: IRBs need to better evaluate the risks and benefits of a trial, but doing so would necessarily be more costly, time-consuming, cumbersome, and demanding for everyone involved since this would entail additional procedures to be standardized for the sake of ethics. We shall argue that this is an artificial predicament; and that this predicament, and also therefore ethical inflation, can be avoided if we look at the issue not simply as an issue of “inflation” but an issue of clarity and transparency of what risk–benefit assessment is, and what tools may be needed to make this evaluation.

The variability in IRB decisions has been well documented and has henceforth stirred ethical discussions. Shah and colleagues (2) have documented the variability of IRB chairpersons' position on the risk categorizations of several interventions such as electromyography and allergy skin testing. Van Luijn and colleagues showed that this variability in risk–benefit identification of IRBs is also largely present in the Netherlands (3-5). In their study, the discrepancy among IRB members on what constitutes risks and what constitutes benefits is again apparent: 100% of the respondents identified and considered “expected or unexpected side-effects and toxicity” as risks, 96% considered the “frequency of visits and stays in hospital and extra visits” as discomfort, but only 65% identified the “psychosocial and social risks” of the trial, and only 20% identified the “decrease in the quality of life” as risk (5).

These statistics on variability not only demonstrate differences in opinion. Again in Van Luijn and colleagues' 2007 study, IRB members mentioned their “inadequate knowledge of the acceptability of certain risks, and (their) inability to imagine the impact of a failed trial-based treatment on the patient/subjects” (4). In their 2006 study, “44% of the IRB members believed that the risks outweighed the benefits or were unable to evaluate the risk-benefit ratio, but only 18% said they would reject the protocol or could not judge its ethical acceptability” (3). If anything, what we see are supposedly risk-benefit judgments that clearly violate the call for either a rational or a proportional balance between risks and benefits, or at the very least, an unclear standard on how this judgment came to be. This is not simply an issue of ethical inflation. These IRBs could have more and more risk and benefit information, but as could already be intuited, more information

does not solve the real problem. An additional tool that may provide more accurate information about risks (such as the RPA tool) only becomes truly useful when its place and its instrumental purpose in the risk-benefit assessment task of IRBs is clear and not plainly routinary, and such could happen only when what risk-benefit assessment means and how this assessment may be done by IRBs is clear.

That IRBs ought to weigh risks against the benefits for the primary purpose of safeguarding the rights and welfare of human subjects, and that risks should never outweigh benefits is something clear. Assuming that it is already clear to the IRB that by risks, they ought to look at not only physical risks and burdens but also social and psychological risks, and that by benefits IRBs need to look at both the direct benefits to the clinical subjects as well as the "importance of the knowledge that may reasonably be expected to result" (6), how should the assessment be done then?

The act of balancing risks versus the benefits cannot remain to be an intuitive task, if we wish IRB deliberations and decisions to be clear, reasonable, transparent, and evaluation-possible. At this point, research ethics needs to acknowledge the deficiency that is yet to be addressed more satisfactorily: how does an IRB balance risks versus the benefits? It would be beneficial to look beyond bioethics and into risk studies and Decision Theory where risk-benefit assessment has been dealt with reasonably. In order to assess the acceptability of risk, i.e., if risks do not outweigh benefits, the "identification, estimation, and evaluation" of risks are necessary (7). Thus, to begin with, it would be necessary for the IRB to *identify and determine*: it would be well to follow the lead of decision theory to make a distinction between "certainty (deterministic knowledge), risk (complete probabilistic knowledge, uncertainty (partial probabilistic knowledge) and ignorance (no probabilistic knowledge)" (8) instead of sticking to the traditional bulky and hazy concept of risk in research ethics. The distinction of these terms and the eventual identification of what the certainties, the risks, the uncertainties and the acknowledged ignorance are in the trial, clarify what truly confronts the IRB, and thus aids in defogging the decision process. Next, in the task of estimating and evaluating risks, Decision Theory may again be of help by providing tools, i.e., decisional matrices, to choose from which allows for a more orderly and reasoned representation of the weighing and evaluation of possible courses of action, given probabilities (if known) and states of nature. Of course, in agreement with contextualist risk theorists, no decision theory representation is satisfactory without the explicit acknowledgement that context as well as values play a role in this evaluatory process, and thus, an ethically weighted risk-benefit analyses that puts forth different matrices based on the decision-makers' explicit dominant values (9) becomes very useful in the deliberation and decision-making process.

Thus, the issue about ethical inflation and the predicament earlier stated can be better dealt with if we look at the issue not simply as an inflation issue but an issue of clarity and reasonableness. In this task, research ethics could truly benefit from the inputs

of Decision Theory and risk studies in risk-benefit assessment. If we see the risk issue this way, the problems about cost, time, and burdens become secondary.

Reference List

(1) Burris S, Davis C. Assessing social risks prior to commencement of a clinical trial: due diligence or ethical inflation? Am J Bioeth 2009 November;9(11):48-54.

(2) Shah S, Whittle A, Wilfond B, Gensler G, Wendler D. How do institutional review boards apply the federal risk and benefit standards for pediatric research? JAMA 2004 January 28;291(4):476-82.

(3) Van Luijn HE, Aaronson NK, Keus RB, Musschenga AW. The evaluation of the risks and benefits of phase II cancer clinical trials by institutional review board (IRB) members: a case study. J Med Ethics 2006 March;32(3):170-6.

(4) Van Luijn HE, Musschenga AW, Keus RB, Aaronson NK. Evaluating the risks and benefits of phase II and III cancer clinical trials: a look at Institutional Review Board members in the Netherlands. IRB 2007 January;29(1):13-8.

(5) Van Luijn HE, Musschenga AW, Keus RB, Robinson WM, Aaronson NK. Assessment of the risk/benefit ratio of phase II cancer clinical trials by Institutional Review Board (IRB) members. Ann Oncol 2002 August;13(8):1307-13.

(6) National Institutes of Health (US). Regulations and Guidelines on the Protection of Human Subjects. 2005.

(7) Bradbury J. The policy implications of differing concepts of risks. Science, Technology, & Human Values 1989;14(4):380-99.

(8) Hansson SO. Decision theory: a brief introduction. Stockholm: Royal Institute of Technology; 2005.

(9) Shrader-Frechette K. Risk and rationality: philosophical foundations for populist reforms. Berkeley, Los Angeles, Oxford: University of California; 1991.

Chapter 6

THE RISK-BENEFIT TASK OF RESEARCH ETHICS COMMITTEES:

AN EVALUATION OF CURRENT APPROACHES AND THE NEED TO INCORPORATE DECISION STUDIES METHODS

R. D. Bernabe, G. J. van Thiel, J. A. Raaijmakers, and J. J. van Delden. The risk-benefit task of research ethics committees: an evaluation of current approaches and the need to incorporate decision studies methods. BMC.Med.Ethics 13:6, 2012.

Abstract

Research ethics committees (RECs) are tasked to assess the risks and the benefits of a trial. Currently, two procedure-level approaches are predominant, the Net Risk Test and the Component Analysis. By looking at decision studies, we see that both procedure-level approaches conflate the various risk-benefit tasks, i.e., risk-benefit analysis, risk-benefit evaluation, risk treatment, and decision making. This conflation makes the RECs' risk-benefit task confusing, if not impossible. We further realize that RECs are not meant to do all the risk-benefit tasks; instead, RECs are meant to evaluate risks and benefits, appraise risk treatment suggestions, and make the final decision. As such, research ethics would benefit from looking beyond the procedure-level approaches and allowing disciplines like decision studies to be involved in the discourse on RECs' risk-benefit task.

I. Background

Research ethics committees (RECs) are tasked to do a risk-benefit assessment of proposed research with human subjects for at least two reasons: to verify the scientific/social validity of the research since an unscientific research is also an unethical research; and to ensure that the risks that the participants are exposed to are necessary, justified, and minimized (1).

Since 1979, specifically through the Belmont Report, the requirement for a "systematic, nonarbitrary analysis of risks and benefits" has been called for, though up to the present, commentaries about the lack of a generally acknowledged suitable risk-benefit assessment method continue (1). The US National Bioethics Advisory Commission (US-NBAC), for example, stated the following in its 2001 report on Ethical and Policy issues in Research Involving Human Participants:

> An IRB's[7] assessment of risks and potential benefits is central to determining that a research study is ethically acceptable and would protect participants, which is not an easy task, because there are no clear criteria for IRBs to use in judging whether the risks of research are reasonable in relation to what might be gained by the research participant or society (2).

The lack of a universally accepted risk-benefit assessment criteria does not mean that the research ethics literature says nothing about it. Within this same 2001 report, the US-NBAC recommended Weijer and Miller's Component Analysis to RECs in evaluating clinical researches. As a reaction to Weijer and P. Miller, Wendler and F. Miller proposed the Net Risk Test. For convenience sake, we shall use the term "procedure-level approaches" (3) to refer to the models of Weijer et al. and Wendler et al.

In spite of their ideological differences, both procedure-level approaches are procedural in the sense that both approaches propose a step-by-step process in doing the risk-benefit assessment. In this paper, we shall not tackle their differences; rather, we are more interested in their similarities. We are of the position that both approaches fall short of providing an evaluation procedure that is systematic and nonarbitrary precisely because they conflate the various risk-benefit tasks, i.e., risk-benefit analysis, risk-benefit evaluation, risk treatment, and decision making (4-6). As such, we recommend clarifying what these individual tasks refer to, and to whom

[7] An institutional review board (IRB) is synonymous to an ethics committee. For consistency's sake, we shall use REC throughout this paper.

these tasks must go. Lastly, we shall assert that RECs would benefit by looking into the current inputs of decision studies on the various risk-benefit tasks.

II. The procedure-level approaches

Charles Weijer and Paul Miller's Component Analysis (Figure 1) requires research protocol procedures or "components" to be evaluated separately, since the probable benefits of one component must not be used to justify the risks that another component poses (2). In this system, RECs would need to make a distinction between procedures in the protocol that are with and those that are without therapeutic warrant since therapeutic procedures would need to be analyzed differently compared to those that are non-therapeutic. It works on the assumption that a therapeutic warrant, that is, the reasonable belief that participants may directly benefit from a procedure, would justify more risks for the participants (7). As such, therapeutic procedures ought to be evaluated based on the following conditions, in chronological order: that clinical equipoise exists, that is, that there is an "honest professional disagreement in the community of expert practitioners as to the preferred treatment" (8); the "procedure is consistent with competent care; and risk is reasonable in relation to potential benefits to subjects" (7). Non-therapeutic procedures, on the other hand, would need to be evaluated on the following conditions: the "risks are minimized and are consistent with sound scientific design; risks are reasonable in relation to knowledge to be gained; and if vulnerable population is involved, (there must be) no more than minor increase over minimal risk" (7). Lastly, the REC would need to determine if both therapeutic and non-therapeutic procedures are acceptable (7). If all components "pass", then the "research risks are reasonable in relation to anticipated benefits" (7).

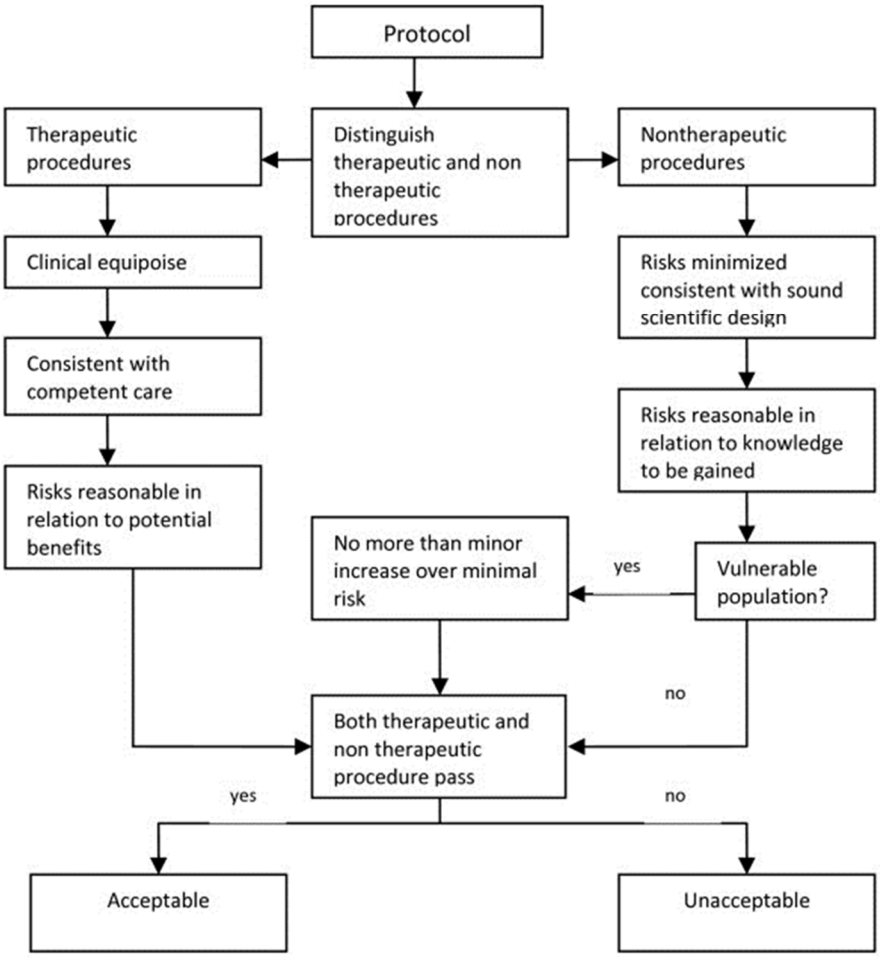

Figure 1: Component Analysis [7,9]

David Wendler and Franklin Miller, on the other hand, developed the Net-Risk Test (Figure 2) as a reaction to the Component Analysis. This system requires RECs to first "minimize the risks of all interventions included in the study" (10). After which, the REC ought to review the remaining risks by first looking at each intervention in the study, and evaluating if the intervention "offers a potential for clinical benefit that compensates for its risks and burdens" [10]. If an intervention does offer a potential benefit that can compensate for the risks, then the intervention is acceptable; otherwise, the REC would need to determine whether the net risk is "sufficiently low and justified by the social value of the intervention" (10). By net risk, they refer to the

"risks of harm that are not, or not entirely, offset or outweighed by the potential clinical benefits for participants" (11). If the net risks are sufficiently low and are justified by the social value of the intervention, then the intervention is acceptable; otherwise, it is not. Lastly, the REC would need to "calculate the cumulative net risks of all the interventions…and ensure that, taken together, the cumulative net risks are not excessive" (10).

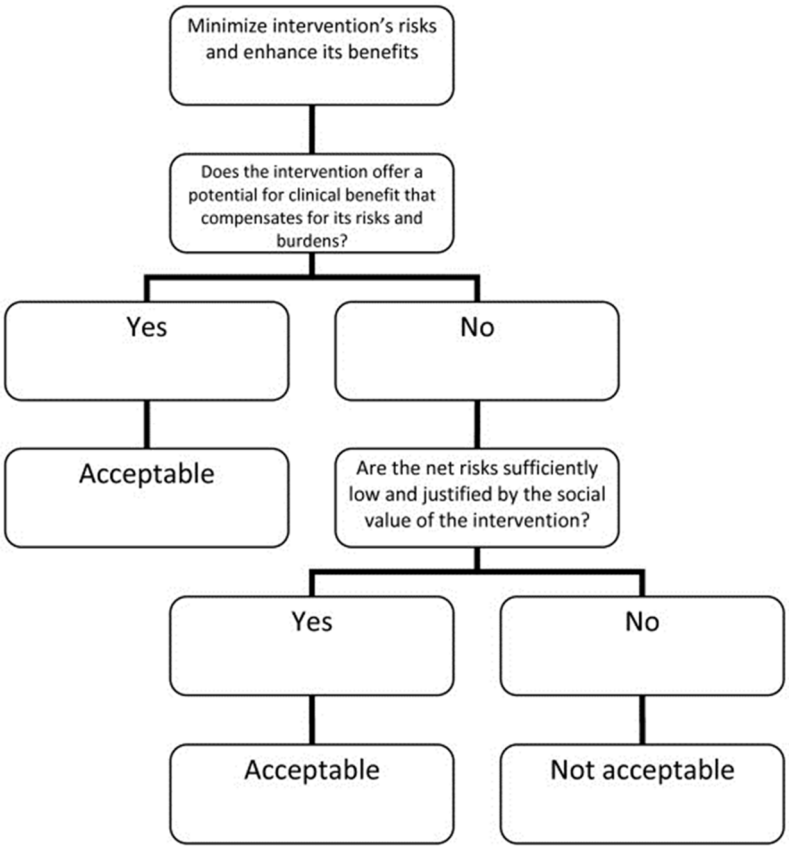

Figure 2: The Net Risk Test [10]

Recently, Rid and Wendler elaborated the Net Risk Test through a seven-step framework (see Figure 3) that is meant to offer a chronological, "systematic and comprehensive guidance" for the risk-benefit evaluations of RECs (11). As we could see from Figure 3, most of the steps are the same as that of the previously explained Net Risk Test; the main addition of the framework is the first step, which is to ensure and enhance the study's social value. In this first step, Rid and Wendler meant that

RECs, at the start of their risk-benefit evaluation, ought to "ensure the study methods are sound"; "ensure that the study passes a minimum threshold of social value"; and "enhance the knowledge to be gained from the study" (11). It is only after the social value of the study has been identified, evaluated, and enhanced could the RECs identify the individual interventions and then go through the other steps, i.e., the steps we have earlier discussed in the Net Risk Test.

Step 1: Ensure and enhance the study's social value
Step 2: Identify the research interventions
Step 3: Evaluate and reduce the risks to participants
Step 4: Evaluate and enhance the potential benefits for participants
Step 5: Evaluate whether the interventions pose net risks
Step 6: Evaluate whether the net risks are justified by the potential benefits of other interventions
Step 7: Evaluate whether the remaining net risks are justified by the study's social value

Figure 3: Seven-step framework for risk-benefit evaluations in biomedical research [11]

III. The procedure-level approaches and the conflation of risk-benefit analysis, risk-benefit evaluation, risk treatment, and decision making

These procedure-level approaches may be credited for providing some form of a framework for the risk-benefit assessment tasks of RECs. They have also provided RECs with a framework that includes and puts into perspective certain ethical concepts that may or may not have been considered in REC evaluations, but are now procedurally necessary concepts. Weijer and Miller, for example, made it necessary for RECs to always consider therapeutic warrant, equipoise, and minimal risk when evaluating the risk-benefit balance of a study. Wendler and Miller on the other hand, provided RECs with the concept of net risk. In spite of these contributions, these approaches presuppose (maybe unwittingly) that risk-benefit analysis, risk-benefit evaluation, risk treatment, and decision making can all be conflated. This, in our view, is a major error that ought to be corrected since from this error flow other problems, problems that unavoidably make the procedures unsystematic and arbitrary. To substantiate our view, we first have to make a necessary detour by discussing the distinction between risk-benefit analysis, risk-benefit evaluation, risk treatment, and decision making (4,5). After which, we shall show how the conflation is present in the procedure-level approaches and how such a conflation leads to difficult problems.

A. Distinction between risk-benefit analysis, risk-benefit evaluation, risk treatment, and decision making

Decisions on benefits and risks in fact involve four activities: risk-benefit analysis, risk-benefit evaluation, risk treatment, and decision making (4-6). In the current debate, these terms are used as if they are interchangeable. Precisely because these four activities have four different demands, it must be made clear that the problem is not merely on terminological preference; that is, the problem cannot be solved by simply "agreeing" to use one term over another. In risk studies, the risk-benefit task concretely demands four separate activities (4,6). Hence, these terms are not interchangeable, and their order must be chronological. The distinctions among these tasks and the necessity of their chronological ordering are as follows.

Risk-benefit analysis refers to the "systematic use of information to identify initiating events, causes, and consequences of these initiating events, and express risk (and benefit)" (4). This, risk-benefit analysis refers to 1.) gathering of risk and benefit events, causes, and consequences; and 2.) presenting this wealth of information in a systematic and comprehensive way, in accordance with the purpose why such information is systematized in the first place. There are a number of risk analysis methods such as fault tree analysis, event tree analysis, Bayesian networks, Monte Carlo simulation, and others (4). The multi criteria decision analysis (MCDA) method, mentioned by the EU Committee for Medicinal Products for Human Use (CHMP) in the *Reflection Paper on Benefit Risk Assessment Methods in the Context of the Evaluation of Marketing Authorization Applications of Medicinal Products for Human Use* (12), proposes the use of a value tree in analyzing the risk-benefit balance of a drug, for example. Adjusted to drug trials, a drug trial risk-benefit analysis value tree could look like (Figure 4).

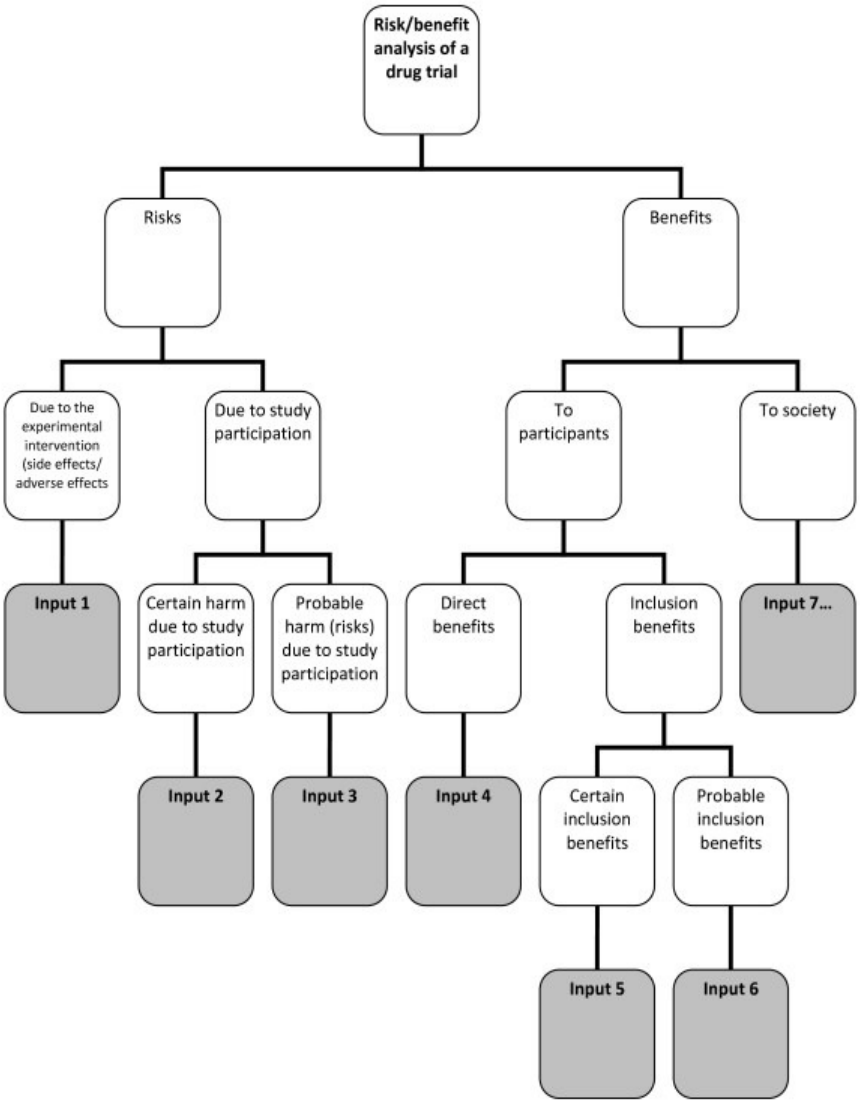

Figure 4: Risk-benefit analysis value tree

In this value tree (Figure 4), we used King and Churchill's typology of harms and benefits (1). From each of the branches, the risk analyst would fill in information about a specific study. Of course, there could be more than one input under each category, depending on the nature of the drug trial being analyzed. Also, this value tree serves as an example; this is not the only way that benefits and risks may be

analyzed within the context of drug trials. The best way to analyze risks and benefits within this context is something that ought to be further discussed and developed. Our aim is simply to show that a method such as a value tree is capable of encapsulating and framing the multidimensional nature of the causes and consequences of the benefits and risks of a study within one "tree." This provides a functional risk-benefit picture from which the risks and the benefits may be evaluated, i.e., risk-benefit evaluation.

Risk-benefit evaluation refers to the "process of comparing risk (and benefit) against given risk (and benefit) criteria to determine the significance of the risk (and the benefit)" (4). There are a number of methods to evaluate benefits and risks. Within the MCDA model for example, the "identification of the risk-benefit criteria; assessment of the performance of each option against the criteria; the assignment of weight to each criterion; and the calculation of the weighted scores at each level and the calculation of the overall weighted scores" (13) would constitute risk evaluation. The multriattribute utility theory (MAUT) is yet another example of an evaluation method. The MAUT is a theory that is basically "concerned with making tradoffs among different goals" (14). This theory factors in human values, values defined as "the functions to use to assign utilities to outcomes" (14). From the value tree "inputs," the evaluator would then need to assign weights to each of these inputs. The purpose of plugging in weights is to establish the importance of each input, according to the evaluators. This is tantamount to establishing criteria, or identifying and making explicit the evaluators' definition of acceptable risk. Next, the evaluators would need to plug in numerical values as the utility values of those that are being evaluated. These values would be multiplied to the weight. The latter values, when summed, would constitute the total utility value. To illustrate, if, for example, an REC wishes to make an evaluation of a psychotropic study drug and the standard drug, an REC may come up with MAUT chart like (Table 1).

	Input 1: Grave adverse effects	Input 2: Trigger secondary psychologi-cal problems	Input 3: Suicidal ideation	Input 4: Safety with younger patients	Input 5: Dosage	Input 6: Adminis-tration…	TOTAL UTILITY
Study drug	50	40	90	50	100	100	50 (1)+ 40 (1) + 90 (.9) + 50 (.5) + 100 (.4) + 100 (.4) + …
Standard drug	70	80	40	100	100	50	70 (1) + 80 (1) + 40 (.9) + 100 (.5) + 50 (.4) + …
WEIGHT	1.0	1.0	.9	.5	.4	.4	

Table 1: MAUT risk-benefit evaluation

Just like the value tree, our purpose is not to endorse only one way of doing the evaluation. Our purpose is merely to illustrate that such a decision study tool is capable of explicitly showing the following: a.) the inputs that the evaluators think must play a role in the evaluation; b.) the values of the evaluators, through the scores they have provided; c.) the importance they give to each of the factors/inputs through the weights that they have provided, d.) how the things compared (in this case, the study drug and the standard drug) fare given a, b and c; and e.) a global perspective of what a, b, c, and d amount to, i.e., through the total utility value.

In the risk-benefit literature in research ethics, we find statements that such an algorithm is undesirable because it "yields one and only one verdict about the risk-benefit profile of each possible protocol" (11). On this issue, CMHP's Reflection is instructive. The scores in quantitative evaluations are valuable not because of some absolute value, but because these scores can

> …focus the discussion by highlighting the divergences between the assessors and stakeholders concerning choice for weights. The benefit of such analysis methods is that the degree and nature of these divergences can be assessed, even in advance of any compound's review. The same method might be used with the weights (e.g., of different stakeholders) and make both the differences and the consequences of those differences more explicit. If the analyses agree, decision-makers can be more comfortable with a decision. If the analyses disagree, exact sources of the differences in view will be identified, and this will help focus the discussion on those topics (12).

Thus, the scores are meant to allow the evaluators to know each others' values, similarities, differences, and divergences. The divergences and differences could aid in focusing the REC discussion and figure out problem areas in a deliberate, transparent, coherent, and less intuitive manner (15).

Risk-benefit analysis and evaluation together constitute risk-benefit assessment (4).

Once risks and benefits have been evaluated versus the evaluators' given criteria, risk evaluation allows evaluators to decide "which risks need treatment and which do not" (6). In decision studies, amplifying benefits and modifying risks are possible only after a global understanding of it through risk assessment has been achieved. Thus, after risk-benefit assessment comes risk treatment. By *risk treatment*, we refer to the "process of selection and implementation of measures to modify risk…measures may include avoiding, optimizing, transferring, or retaining risk" (4). In terms of trials, risk treatment would refer to enhancing the trial's social value, reducing the risks to the participants, and enhancing the participants' benefits (11). There may be concerns especially from REC members who have been used to minimizing risk immediately after its identification that this process necessitates them to suspend such move until risk evaluation is done, a procedure that may be counter-intuitive for some. However, the process of "immediately cutting the risks" also have passed through the process of evaluation, although intuitively and implicitly. An REC member who says that the risks of a certain procedure may be minimized or that the risks are unnecessary given the research question has already implicitly gone through a personal evaluation of what is and what is not necessary in such a clinical trial.

After investigating on the possibilities to modify risk and amplify the benefits, the decision makers would then have to finally decide whether the risks of the trial are justified given the benefits. By *decision making*, we refer to the final discussion of the REC on whether benefits truly outweigh risks, i.e., given all the information provided, are the risks of the trial ethically acceptable due to the merits of the probable benefits?

It is important to note that in the risk literature (4,13), the CHMP Reflection (12), and the CIOMS report (16), the risk-benefit tasks are assumed to be done interdependently and that the tasks are reflective of various values, interests, and ethical perspectives. At least for marketing authorization and marketed drug evaluation purposes, the sponsor and/or the investigator are assumed to be responsible for risk-benefit assessment and to a certain extent, the proposal of risk treatment measures. It makes a lot of sense that the sponsor ought to be responsible for risk analysis precisely because in this task, "experts on the systems and activities being studied are usually necessary to carry out the analysis" (4). The regulatory

authorities, on the other hand, are expected to provide guidelines for the risk-benefit analysis criteria. They also ought to provide their own version of risk-benefit evaluation to determine areas of divergences and differences, to extensively discuss risk treatment measures and options, and finally to deliberate and decide based on all these inputs.

B. Conflation of the various risk-benefit tasks by the procedure-level approaches

At the most superficial level, we notice that Wendler and Rid used the terms "risk-benefit assessment" and "risk-benefit evaluation" interchangeably to refer to the one and the same Net Risk Test (11,17). Nevertheless, it could be argued that this is just a matter of misuse of terms, and that such does not substantially affect the approach that is proposed. Thus, we would need to look deeper into the Net Risk Test to justify our claim that it conflates the various risk-benefit tasks.

In the latest seven-step framework of the Net Risk Test, what ought to be a framework for risk-benefit evaluation of RECs ended up incorporating aspects of risk-benefit assessment, risk treatment, and decision making. The first step, that is, ensuring and enhancing the study's social value, is risk treatment. The second step, that is, identifying the research interventions, is risk analysis. The third and fourth steps, which are the evaluation and reduction of risks to participants, and the evaluation and enhancing of potential benefits to participants, both fall into risk-benefit evaluation and risk treatment. It is worthwhile to note that in the Net Risk Test, the evaluation and the treatment of risks and benefits were not preceded by the identification of these risks and benefits; instead, prior to the third and fourth steps is the step to identify research interventions, a necessary but incomplete step in risk-benefit analysis. The fifth step, that is, the evaluation whether the interventions pose net risks, is risk-benefit evaluation. The sixth step, which is to evaluate whether the net risks are justified by the potential benefits of other interventions, is decision making. The last step, which is to evaluate whether the remaining net risks are justified by the study's social value, is also decision making. Thus, the Net Risk Test in principle encompasses all the risk-benefit tasks without taking into account the distinctions, the chronological order among the various tasks, nor the division of labor in the various risk-benefit tasks.

Component Analysis, just like the Net Risk Test, does the same conflation. In the process of distinguishing procedures into either therapeutic or non-therapeutic, the REC members would first need to identify the procedures to assess, i.e., risk analysis. The REC members would then need to evaluate therapeutic procedures differently compared to non-therapeutic procedures. Therapeutic procedures have to be evaluated on whether clinical equipoise exists, and whether the procedure is consistent with competent care. These two criteria may be considered as ethical

principles that ought to be present in the deliberation towards decision making. Thus, these are decision making tasks. Next, the REC members would need to determine if the therapeutic procedure is reasonable in relation to the potential benefits to subjects. Since REC members need to answer questions of "reasonability," this is a decision making task that presupposes risk-benefit evaluation. Non-therapeutic procedures, on the other hand, would necessitate the assessor to evaluate if risks are minimized and if risks are consistent with sound scientific design. This is risk treatment. Next, the assessor would need to verify if the risk of the non-therapeutic procedure is reasonable in relation to knowledge to be gained. Again, this is a decision making task that presupposes risk-benefit evaluation. In cases where vulnerable patients are involved, the REC members would need to verify if no more than minor increase over minimal risk is involved; this is a discussion that is likely to be present in the deliberation towards decision making, which also presupposes risk-benefit evaluation. Lastly, the assessor would need to make a decision if both therapeutic and non-therapeutic procedures pass. This is decision making. Hence, again, what we have is a system that touches on each of the risk-benefit tasks without making a distinction among the various tasks.

Since the risk-benefit tasks are conflated, the various tasks are necessarily simplified and confused. We have seen that the various risk-benefit tasks are resource intensive (since various experts must be involved), necessarily complex (since a drug trial is rarely simple), and time consuming. This is the reason why they are done separately. To conflate the various tasks into one system that ought to be accomplished within the few hours that the REC convenes is an impossibility. Precisely because of this conflation, plus the consideration that all the risk-benefit tasks ought to be done within the time restrictions of an REC, both procedure-level approaches cursorily and confusedly "accomplish" the various tasks. As such, we cannot expect the procedure-level approaches to have the same level of robustness, transparency, explicitness, and coherence as the various approaches of decision studies have. Neither of the procedure-level approaches could have the same robustness that the value-tree had, for example, in expressing and illustrating the relations between the nature, cause, consequences, as well as the uncertainties, of both risk and benefit components. Neither is also transparent, explicit, and rigorous enough to capture the acceptable risk definitions and the various weights and scores that are reflective of the various values and ethical dispositions that the MAUT method provided. The two procedure-level approaches simply do not require evaluators to be explicit in terms of their evaluative values. Though risk treatment is largely present in both procedure-level approaches, risk treatment, at least in the Net Risk Test, is sometimes confounded with risk evaluation. In the procedure-level approaches, RECs would also not have the benefit of systematically focusing the

discussion on divergences and differences that a good risk evaluation makes possible. Lastly, because of the conflation and confusion of the various risk-benefit tasks, REC members are left to their own devices and intuition to decide on what is important to discuss and which is not, and eventually, to decide if the risks are justifiable relative to the benefits. Such a "procedure" could be categorized as a "taking into account and bearing in mind" process, a process that Dowie rightfully criticized as vague, general, and plainly intuitive (15).

IV. **Recommendations**

We have seen that the methods from decision studies are more robust, transparent, and coherent than any of the procedure-level approaches. This is not surprising considering the fact that decision studies have been utilized in many various fields for quite some time now. The robustness of the decision studies methods stems from the clear distinction between risk-benefit analysis, risk-benefit evaluation, risk treatment, and decision making. In decision studies, each of the risk-benefit tasks is a system in itself that ought not to be conflated. In addition, in contrast to "taking into account and bearing in mind" processes, decision studies encourage the exposure of beliefs and values (15) precisely because it is from this explicitness that discussions can be defined and ordered. As such, we recommend the following:

A. RECs should make clear what their task is. RECs do not have the time and are not in the best position to do risk analyses. As such, risk analysis must be a task for the sponsor. As regards risk evaluation, RECs ought to provide their own risk-benefit evaluation to pair with the sponsor's/investigator's evaluation since this is the best way to systematically point out areas of divergence/convergence. These areas would aid in putting order in REC discussions. The evaluation of risk treatment suggestions and possibly coming up with a revised or different risk treatment appraisal ought to also form part of REC discussions. Lastly, it is obviously the REC's task to make the final decision on whether the risks of the trial are justified given the benefits.
B. Precisely because such a clarification of tasks is so essential if the REC is to function efficiently, RECs must look into how decision studies may be incorporated in its risk-benefit tasks. This is something we will do in the next chapter. For now, it is imperative to lay the theoretical groundwork for the urgency of such incorporation.
C. The procedure-level approaches emphasize on the role of the various ethical concepts such as net risk, minimum risk, clinical equipoise, in the risk-benefit task of RECs. These are legitimate concerns; nevertheless, RECs must know when these concepts play a role in the various risk-benefit tasks. Minimal risk, for

example, is a concept that ought to be present in risk treatment and/or deliberation towards final decision making.

V. Conclusion

Both the Net Risk Test and the Component Analysis conflate risk-benefit analysis, risk-benefit evaluation, risk treatment, and decision making. This makes the risk-benefit task of RECs confusing, if not impossible. It is necessary to make a distinction between these four different tasks if RECs are to be clear about what their task truly is. By looking at decision studies, we realize that RECs ought to evaluate risks and benefits, appraise risk treatment suggestions, and make the final decision. Further clarification and elaboration of these tasks would necessitate research ethicists to look beyond the procedure-level approaches. It further requires research ethicists to allow decision studies discourses into the current discussion on the risk-benefit tasks of RECs. Admittedly, this would take a lot of time and research effort. Nevertheless, the discussion on the REC's risk-benefit task would be more fruitful and democratic if research ethics opens its doors to other disciplines that could truly help clarify risk-benefit task distinctions.

Reference List

(1) King NM, Churchill LR. Assessing and comparing potential benefits and risks of harm. In: Emanuel E, Grady C, Crouch RA, Lie RA, Miller FG, Wendler D, editors. The Oxford textbook of clinical research ethics.New York: Oxford University Press; 2008. p. 514-26.

(2) US National Bioethics Advisory Commission. Ethical and Policy issues in Research Involving Human Participants. 2001.

(3) Westra AE, de Beufort ID. The merits of procedure-level risk-benefit assessment. IRB: Ethics and Human Research 2011.

(4) Aven T. Risk analysis: asssessing uncertainties beyond expected values and probabilities. Chichester: Wiley; 2008.

(5) Vose D. Risk analysis: a quantitative guide. 3rd ed. Chichester: John Wiley & Sons; 2008.

(6) European Network and Information Security Agency. Risk assessment. 2012.

(7) Miller P, Weijer C. Evaluating benefits and harms in clinical research. In: Ashcroft RE, Dawson A, Draper H, McMillan JR, editors. Principles of Health Care Ethics, Second Edition. Wiley & Sons; 2007.

(8) Weijer C, Miller PB. When are research risks reasonable in relation to anticipated benefits? Nat Med 2004 June;10(6):570-3.

(9) Weijer C. The ethical analysis of risk. J Law Med Ethics 2000; 28:344–361.

(10) Wendler D, Miller FG. Assessing research risks systematically: the net risks test. J Med Ethics 2007 August;33(8):481-6.

(11) Rid A, Wendler D. A framework for risk-benefit evaluations in biomedical research. Kennedy Inst Ethics J 2011 June;21(2):141-79.

(12) European Medicines Agency -- Committee for Medicinal Products for Human Use. Reflection paper on benefit-risk assessment methods in the context of the evaluation of marketing authorization applications of medicinal products for human use. 2008.

(13) Mussen F, Salek S, Walker S. Benefit-risk appraisal of medicines. Chichester: John Wiley & Sons; 2009.

(14) Baron J. Thinking and deciding. 4th ed. New York: Cambridge University Press; 2008.

(15) Dowie J. Decision analysis: the ethical approach to most health decision making. In: Ashcroft RE, Dawson A, Draper H, McMillan JR, editors. Principles of Health Care Ethics. John Wiley & Sons; 2007. p. 577-83.

(16) Council for International Organizations of Medical Sciences's Working Group IV. Benefit-risk balance for marketed drugs: evaluating safety signals. 1998.

(17) Rid A, Wendler D. Risk-benefit assessment in medical research-- critical review and open questions. Law, Probability and Risk 2010;9:151-77.

Chapter 7

DECISION THEORY AND THE EVALUATION OF RISKS AND BENEFITS OF CLINICAL TRIALS

R. D. Bernabe, G. J. van Thiel, J. A. Raaijmakers, and J. J. van Delden. Decision theory and the evaluation of risks and benefits of clinical trials. Drug Discov.Today 17 (23-24):1263-1269, 2012.

Abstract

Research ethics committees (RECs) are tasked to assess the risks and the benefits of a clinical trial. In previous studies, it was shown that RECs find this task difficult, if not impossible, to do. The current approaches to benefit-risk assessment (i.e. Component Analysis and the Net Risk Test) confound the various risk-benefit tasks, and as such, make balancing impossible. In this article, we show that decision theory, specifically through the expected utility theory and multiattribute utility theory, enable for an explicit and ethically weighted risk-benefit evaluation. This makes a balanced ethical justification possible, and thus a more rationally defensible decision making.

I. Introduction

Research ethics committees (RECs) are tasked to assess risks and benefits of a study (1), and in the process determine if "the importance of the objective (of the study) outweighs the inherent risks and burdens to the research subjects" (2). This statement from the Helsinki Declaration is supported by various ethical guidelines and directives such as the CIOMS *International Ethical Guidelines for Biomedical Research Involving Human Subjects*, section 8 (3), the *Belmont Report*, section D.2 (1), the WHO *Operational Guidelines for Ethics Committees that Review Biomedical Research*, section 6.2.1.2 (4), and the EU Directive 2001/20/EC, Article 3 section 2.a (5). There may be variations on how to interpret the quote from the WMA Declaration of Helsinki, such as whether "objectives" refers to both societal benefits and benefits to the participants, or to only one of these benefits, but one thing is clear: that RECs are tasked to ensure that benefits and risks are reasonably balanced, that is, that benefits outweigh risks. Such a balancing is required for at least two reasons: to verify the scientific and social validity of the research; and to protect the participants from undue harm (6).

Among the various tasks of RECs, the assessment of risks and benefits proves to be one of the most difficult tasks. In a series of studies on RECs in the Netherlands, van Luijn et al. demonstrated the following:

(i) that REC members felt they were not competent to do the task;

(ii) only a small minority do some sort of systematic evaluation of risks and benefits;

(iii) one-third of REC members leave the task of determining the risk-benefit ratio to the patients;

(iv) the lack of criteria to make the risk-benefit assessment and the uncertainty about the benefits to patients and the rationale of the study provide the most difficulty when doing the assessment;

(v) REC members felt they need additional courses on risk-benefit assessment; and

(vi) REC members felt they would benefit from the additional knowledge about the trial experience and perceptions of patients, and from having a clear understanding of the researcher's risk-benefit assessment of the study (7- 9).

In the research ethics literature, two risk-benefit assessment approaches are dominant: the Net Risk Test and Component Analysis. In the previous chapter, we have argued that these two approaches, which, following Westra and de Beaufort, we would conveniently call procedure-level approaches (10), conflate the various risk-benefit tasks, and in doing so, they make the task of risk-benefit assessment difficult to accomplish (11). Apart from the conflation, these approaches do not help in resolving how to do the balancing in the first place. For example, according to Component Analysis, RECs are required to provide a "yes" or a "no" response on whether, in a therapeutic procedure, the risks are reasonable 'in relation to potential benefits'; or whether "risks are reasonable in relation to knowledge to be gained" in a nontherapeutic procedure (12, 13). What "reasonable" means and how to determine reasonability is not explained and thus left to the often unexpressed intuitions of the REC members. By intuition, we refer to "judgment made directly without looking for reasons" (14). The Net Risk Test leaves as much work to the intuition of the REC members. It requires REC members to determine if an "intervention offers a potential for clinical benefit that compensates for the risks and burdens" and, in studies with no potential benefit, if the "net risks are sufficiently low and justified by the social value of the intervention" (15).

Acknowledging the contribution of procedure-level approaches in identifying and including various ethical principles such as equipoise and net risk within the framework of risk-benefit assessment, it remains a fact that these approaches do not provide further guidance on how to do the balancing (i.e. on how to provide a "yes" or a "no" response on the pivotal questions on risk reasonability or the justifiability of the net risks). The terms "compensate," "sufficiently low," "reasonable" and "justified" are heavily normative words that would leave even seasoned ethicists arguing without end. In addition, even if these terms would leave REC members unperturbed, the lack of guidance on how to proceed with the balancing of the risks and the benefits in an explicit, transparent, and consistent manner would push RECs to resort to unelaborated and unprocessed intuitions. This brings us back to the problem stated by van Luijn et al. about the lack of systematic method to do the balancing of benefits and risks. As such, it is doubtful that the procedure-level approaches, in their current versions, are able to deal with the REC problems that van Luijn et al. presented.

Recently, the European Medicines Agency (http://www.ema.europa.eu/ema/) launched a benefit-risk methodology project that aims to "identify decision-making models that can be used in the Agency's work, to make the assessment of the benefits and risks of medicines more consistent, more transparent and easier to audit" (16). Within this project, there were several observations, recommendations, and conclusions, among which are the following.

First, model-based, structured approaches to problem solving are capable of avoiding and correcting errors and biases brought about by intuitive aggregation. In addition, such approaches can aid in deriving solutions that were not initially apparent to the participants (17).

Second, only decision theory is capable of explicitly incorporating "the three key ingredients of benefit-risk assessments," which are the following: data on benefits and risks, the uncertainties, and 'clinical judgments about the desirability, severity, and relevance of the effects' (18).

Indeed, there is substantial literature on the usefulness of the various methods in decision theory not only in individual decision making to compensate for intuitive aggregation, but also in group decision making as well (19-21). However, we know of no literature that evaluates the performance of RECs in terms of benefit-risk assessment using any method. The empirical proof that decision theory is something that RECs would find useful in performing their task of assessing benefits and risks is something we wish to work on in the future.

We shall assume the findings of the EMA in addition to the findings of the literature that establish the usefulness of decision theory methods in group decision making; we shall further assume the findings of our earlier chapter that RECs would benefit from looking at the resources of decision studies on risk-benefit assessment (11). What we wish to theoretically demonstrate in this paper is decision theory's applicability within the research ethics committee's setting specifically in evaluating the benefits and risks of a pharmaceutical clinical trial. As such, we shall address the following question: how can RECs balance risks and benefits of a pharmaceutical clinical trial in a reasonable manner?

We shall limit ourselves to the evaluation of pharmaceutical clinical trials because at least within the Netherlands and the European Union, clinical trials that test pharmaceutical products are the majority[8]. Given the current drive to stimulate and facilitate the development of innovative drugs (22), it is worthwhile to look at REC benefit-risk assessment within the context of pharmaceutical clinical trials.

[8] We made a search on May 29, 2012 using ClinicalTrials.gov of all registered interventional trials in the Netherlands and the European Union with no date restrictions. In the Netherlands, there were 2262 registered industry-sponsored trials in contrast to 1315 investigator-initiated trials. Of all the sponsor-initiated trials, 2033 tested a pharmaceutical product. Assuming that some of the investigator-initiated trials also test a pharmaceutical product, it is safe to say that clinical trials testing pharmaceuticals are the majority in the Netherlands. In the European Union, there were 41,159 sponsor-initiated trials in contrast to 15,408 investigator-initiated trials. Of all the sponsor-initiated trials, 38,268 test a pharmaceutical product. Considering that some of the investigator-initiated trials also test a pharmaceutical product, pharmaceutical clinical trials are also the majority within the European Union.

Before we address our main question, it would be important to address what decision theory is.

II. What is decision theory?

Decision theory springs from economics, mathematics, philosophy, social science, and statistics (23). It is concerned with "goal-directed behavior in the presence of options" (24). That is, decision theory, as a normative theory, provides guidance on the best option to take, based on the principle of maximized utility. As a descriptive theory, it may also be used to reveal preferences and values.

Decision theory is most famous for its expected utility theory (EUT) and the multiattribute utility theory (MAUT). These theories may be useful in research ethics in general (25). In this article, we aim to demonstrate how EUT and MAUT may be useful in the risk-benefit task of RECs. Before going through these theories, we need to state some of our assumptions.

A. The shared task of risk-benefit evaluation

First, decision theory is concerned with inference and not search (14); hence, before decision theory could be used, it is assumed that the decision maker already has some facts. Of course, since decision theory deals with risks and probabilities, certainty is seldom, if never, assumed. Human decisions are most of the time based on beliefs and incomplete evidences, but decisions need to be made anyway. The same may be said about clinical trials. Because it is a trial, we can never be certain about efficacy and/or safety; however, RECs, based on the best available knowledge, would need to make decisions on the acceptability of a trial.

Because decision theory refers to inference and not search, the theory applies most to risk-benefit evaluation, with the aim of aiding the eventual decision-making. Previously, and in agreement with the literature on risk studies, we have shown that the risk-benefit task in fact refers to four activities: risk-benefit analysis, risk-benefit evaluation, risk treatment, and decision-making (11). Risk-benefit evaluation refers to the "process of comparing risk (and benefit) against given risk (and benefit) criteria to determine the significance of the risk (and the benefit)" (26). It is possible only after information about risks and benefits has been gathered and systematized, that is, after risk-benefit analysis. A transparent and explicit risk-benefit evaluation would greatly aid RECs in making a decision.

We should note that the four tasks are not the sole responsibility of RECs (11). These risk-benefit tasks must be done interdependently and cooperatively such that the sponsor, the investigator, and the RECs work together to optimize the quality of the process (11, 27). We have earlier sketched the distribution of the various benefit-

risk assessment tasks (11). In terms of benefit-risk evaluation, the task that interests us in this chapter, ideally both the sponsor and the REC should make their versions of risk-benefit evaluation. RECs ought to compare their version of risk-benefit evaluation to that which was provided by the sponsor, and in the process identify points of agreement and contention. This would come close to Shrader-Frechette's ethically weighted assessment (28), where various stakeholders provide their versions to bring as much clarity on similarities and differences as possible, and thus aid in a more procedurally democratic process (28). This information could pinpoint differences, which the REC discussion ought to resolve or decide upon.

B. Using numbers in decision making

Second, contrary to the belief that decision theory is about making judgments depend on calculations, as if judgments will have to be done by some mathematical equation that "yields one and only one verdict about the risk-benefit profile of each possible protocol" (29), or that the positive (or negative) results of a decision theory calculation equates to a positive (or negative) protocol (30), the instruments of decision theory use numbers not to replace human decision making. Rather, numbers are used as units of utils as a "summary measure of how consequences realize ultimate values or good" (14). They are means to systematize and make explicit the consequences (in the case of REC evaluations, the risks and the benefits) and the values and preferences of the decision makers.

However, although numbers represent consequences, values, and preferences, the use of numbers also mean that decision theory tools assume simple consistency principles such as the transitivity principle that if A is better than B, and B is better than C, then A is better than C (17). Such consistency principles lead to logical coherence (17); hence, a decision maker who puts 100 utils to option A and 50 utils each to options B and C is saying that option A is equal to options B and C put together. With these in mind, we can now discuss EUT and MAUT.

III. Expected utility theory

EUT is a decision analysis tool that is used in situations that are similar to gambles (15), that is, situations where probabilities are somehow known and utilities, generally defined as numerical representation of human goals, have been determined by the decision maker. Of course, depending on the amount of knowledge already available, probabilities may be more or less accurate. This ought not to stop us from using such probabilities since a decision must be made with the best current knowledge. This dispels concerns about the impracticability of an expected value calculation that allegedly "requires us to know more about the potential effects of

medical research than we usually can" (30). Because EUT works on the best possible knowledge, its calculation does not guarantee a positivist certainty; EUT does not have that pretension. The fact that probabilities are involved unambiguously tells us that EUT works with the context of uncertainty, risks, and probable benefits.

In EUT, "to each alternative is assigned a weighted average of its utility values under different states of nature, and the probabilities of these states are used as weights" (24). Thus, the necessary elements would be the "alternative courses of action," the "utility values" of these alternatives under various states of nature, and the "probabilities" of the different states of nature. Expressed in a mathematical formula, the expected utility value of each alternative course of action is as follows:

$$p_1u_1+p_2u_2+\cdots+p_nu_n$$

where n refers to the number of outcomes, p as the probability of these outcomes, and u as the utility of these outcomes (24).

The u value is determined by using known facts and subjective measures because by utility, we refer to a "summary measure of how consequences realize our ultimate values or goals" (15). However, "subjective" does not mean that anything goes. As mentioned above, a utility value must at least pass through the test of consistency such that measurements between the u values are cardinal (either in a ratio or interval scale (31)) in nature. It is also important that the u value is in fact using a single scale, irrelevant whether direct judgment was used or standard gamble or tradeoff (15). What the ideal utility measurement is for RECs would need to be explored separately, something we obviously cannot do here. For our purposes, it is sufficient to state that in spite of the subjectivity of u values, these values are also not pure random.

Apart from showing the interval values of an act in different states of nature, u is also reflective of other factors that the risk evaluator considers as utilities or disutilities attached to the given act. This means that u is expressive of various details and can "themselves include other options, other states, and so on" (15). Thus, when evaluating the risk acceptability of a specific dosage administration given a specific state of affairs for example, u may be an expression of safety, efficacy, ease of administration, and others. It would be best if the evaluation were expanded in such a manner as to capture and express all these values.

Applied to REC evaluations, using a fictitiously predefined u scale of 1–10, and probability measures that ideally are inputs from the sponsor, an EUT evaluation of a trial drug and a standard comparator may look like Table 1.

	Mildness of adverse event (safety 1)	Mildness of adverse event (safety 2)	Efficacy	Ease of use	Expected utility (EU)
Trial drug	30% (3 u)	40% (4 u)	60% (8 u)	100% (10 u)	(0.3 x 3) + (0.4 x 4) + (0.6 x 8) + (1 x 10) =17.3
Standard comparator	32% (3.1 u)	35% (3.3 u)	62% (8.1 u)	90% (9 u)	(0.32 x 3.1) + (0.35 x 3.3) + (0.62 x 8.1) + (0.9 x 9) =15.27

Table 1: An expected utility table used to evaluate two interventions (the trial drug and the standard comparator) in a clinical trial

From Table 1, the REC members could evaluate among themselves if equipoise exists for example, by looking at the EU values. Equipoise refers to "the state of indifference or disagreement in the expert medical community about the net preferred medically established procedure" (32). As such, roughly, equipoise exists if the EU values of the two interventions are close to each other. Apart from equipoise, this data also gives REC members a good idea of how much utility (or good, or value) they have put on a certain alternative, given a particular state. Hence, the *u* value is indicative of the REC's appreciation (or lack of it) of a specific outcome. Thus, for this REC, the trial drug's ease of use is of the best kind, whereas the standard comparator is close to but not as good as the trial drug's ease of use. Lastly, Table 1 provides the REC with a holistic picture of the two interventions given the various states (safety 1, safety 2, efficacy, ease of use) and the corresponding probabilities. Assuming that the sponsor provides their version of an EU table, RECs could have a focused and transparent discussion on the discrepancies or similarities on the *u* values and the EU scores, and what these discrepancies and/or similarities ethically mean (i.e., how they weigh in the decision process). Apart from the EUT, MAUT is also a promising tool for REC evaluations.

IV. Multiattribute utility theory

In EUT, personal values are assumed to be incorporated in *u* values. In MAUT, values are made explicit through value weights. In the literature, the terms MAUT, multiple criteria decision making, and multi-criteria decision analysis were used to refer to the decision theory method that necessitates the determination of alternatives, of the attributes (also called criteria), of the weights of these attributes, of the *u* values, and

of the total utility value using these factors. As such, at least for our purposes, we would treat these various terms as essentially referring to the same method.

MAUT is a theory that is "concerned with making tradeoffs among different goals" (15). It does this by giving various weights to attributes, in effect making explicit how much a decision maker values an attribute against which an option is evaluated. These weights are multiplied to the utility values of an option. The total utility provides a summary of the utilities of an option, given the individual weights of the attributes. Thus, looking at our example (Table 2), what added value does this provide us? With the EUT, the attributes, as states, were treated equally. Personal values came in with the choice of the attributes and in the specification of *u*, but not in specifying which attribute is more important. In MAUT, this kind of specification is possible. Hence, what we have is a table that captures the hierarchy of values of the decision maker through the weights of the attributes, and the individual evaluation of each outcome of an option through the *u* values. The total utility value gives us a global picture or a summary of the decision maker's hierarchy of values combined with the *u* values. A REC that has this information, coupled with the sponsor's version of a MAUT evaluation, would have an explicit knowledge of the criteria that were used to evaluate the two interventions. As with the EUT, the discussion can then be focused on the variations and/or similarities in utility values and attributes, but also those of attribute weights and total MAUT utility scores. This leads not only to the pointing out of the sources of conflict in terms of *u* values, probabilities, and criteria or attributes between a REC and the sponsor; it would also make the ethical weights known to all the persons concerned. Because these weights provide an ordinal hierarchy of the attributes, these weights may be indicative of the hierarchy of the decision maker's ethical principles, ideologies, and intuitions.

(weights)	Safety 1 (0.8)	Safety 2 (0.8)	Efficacy (1.0)	Ease of use (0.5)	Total utility
Trial drug	3	4	8	10	(3 x 0.8) + (4 x 0.8) + (8 x 1) + (10 x 0.5) = 18.6
Standard comparator	3.1	3.3	8.1	9	(3.1 x 0.8) + (3.3 x 0.8) + (8.1 x 1) + (9 x 0.5) = 17.7

Table 2: Multi-attribute utility theory used to evaluate two interventions (the trial drug and the standard comparator) in a clinical trial

V. MAUT and the benefit-risk evaluation of a clinical trial

MAUT could also be used holistically to aid in evaluating the risks and the benefits of a trial. By now, we probably already have a feel of the necessary steps than a REC would have to take if they are to use MAUT in benefit-risk evaluation. Salo and Hamalainen summarize the phases involved when a group employs MAUT in its evaluation (19). Their phases are not different from the often-quoted PrOACT phases (17, 33). Using Salo and Hamalainen's phases, we can have a better picture of what it would take for an REC to balance benefits and risks using MAUT:

A. Clarification of the decision context and the identification of the group members

Within a REC, the decision context and the group members are not difficult to identify. Context refers to the type of trial (phases I, II, III or IV), the interventions involved, the number of arms, and others. Who does the evaluation is also not difficult to determine. Some laws such as §46.107 of the American Common Rule (34) provide guidance on the number of members and their qualifications. An important consideration in terms of members would be the identification of the other participants other than the decision makers. For example, patient organizations, the sponsor, or health technology assessors may be sources of expertise with whom the decision makers may wish some specific inputs from.

B. Explication of decision objectives

In terms of objectives, benefit-risk evaluation is done to help determine if risks do not outweigh the benefits (i.e., if risks are acceptable in the trial). At this point, REC members would need to identify the criteria or attributes on which to evaluate the trial. An REC for example may wish to use King and Churhill's (6) typology of benefits and harms to evaluate a clinical trial (Box 1).

BENEFITS	RISKS
1. Benefits to participants A. Direct benefits B. Inclusion benefits i. Certain inclusion benefits ii. Probable inclusion benefits 2. Benefits to society	1. Risks due to experimental intervention (side effects) 2. Risks due to study participation A. Certain harm due to study participation B. Risks due to study participation

Box 1: King and Churchill's typology of risks and benefits of a clinical trial

C. Generation of alternatives

The decision alternatives for a REC are the following: approve the trial's balance of benefits and risks (i.e., declare the risks are acceptable given the benefits); reject the balance of benefits and risks; and request for modifications on the current balance of benefits and risks.

Apart from these decision alternatives, it is also necessary to spell out the various interventional alternatives in a clinical trial (i.e., the various arms such as the placebo arm, the experimental drug arm, and the active comparator arm). These arms would be the alternatives that will be scored using *u* values in the MAUT decision table.

Adjusted to the purposes of a REC of balancing the benefits and the risks of a clinical trial, only the interventional alternatives are relevant in the MAUT decision table. This means to say that the decisional alternatives of accepting, rejecting, or modifying the benefit and/or risk balance are conclusions that may partly be deduced from the MAUT decision table; they are not alternatives that belong to the actual decision table.

D. Elicitation of preferences

At this point, the REC members would have to state their preferences in terms of weights of the various criteria or attributes that were previously identified. They would also need to identify the *u* values of the clinical trial in contrast to the attributes.

E. Evaluation of alternatives

The MAUT decision table is used as an instrument to evaluate the clinical trial, along with its various arms. Putting King and Churchill's typology of harms and benefits (6) in a MAUT table with fictitious numerical values that evaluates a two arm trial, we have Table 3 and Table 4.

Risks due to experimental intervention (side effects)		**Risks due to study participation**	
Comparator arm (0.25)	Trial drug arm (0.25)	Certain harm due to study participation (0.25)	**Risks due to study participation (0.25)**
-3	**-4**	**-4**	**-3**

Table 3: Multiattribute utility theory used to evaluate the risks of a clinical trial

Benefits to participants				Benefits to society (0.5)
Direct benefit		Inclusion benefits		
Comparator Arm (0.2)	Trial drug arm (0.2)	Certain inclusion benefit (0.05)	Probable inclusion benefit (0.05)	
3	3	3	3	8

Table 4: Multiattribute utility theory used to evaluate the benefits of a clinical trial

If we look at Table 3 and Table 4, we learn many things not only about the trial but also about the values of the decision maker. For example, the decision maker thinks that the risks due to the experimental intervention are as valuable as the risks due to study participation (because these two broad categories of risks were given the same weight values (i.e., 0.5)); that the benefits to participants weigh as heavy as the benefits to society (again because the weight values of the two broad categories are equal (i.e., 0.5)); and that inclusion benefits must be considered as a benefit but should not be a major consideration (because it was given a weight of 0.10). If we look at the total utility values of both tables, the total value of the risk table is −3.5 and of the benefit table is 5.5. Putting the two together, that would be 5.5 − 3.5 = 2. The positive value allows the REC to deduce that based on their personal values, the benefits outweigh the risks.

F. Synthesis

Creation of the decision table is a huge step in making the decision makers' preferences, values, trade-offs explicit, and the facts at hand. In the EMA study on the usefulness of decision theory methods to regulators, the participants felt that the exercises on decision modeling "helped to develop new insights, realigning intuitions and creating a common purpose among participants." Ideally, the completion of the MAUT table should mark the end of the benefit-risk evaluation process. The RECs at this point should be ready for the final step (i.e. decision-making). However, it may be possible that REC members still feel there is something missing, that there is something wrong with the table, that the sponsor's version of evaluation conflicts with REC's version, or that other factors need to be considered in the benefit-risk balance. Before the final decision is made, these "loose ends" would have to be factored in. For example, disagreements with the decision table would have to be

discussed by pointing out specific areas of concern. In the EMA study, they found that the tables were most useful during disagreements or misalignments because the "(decision theory) model provided a framework for clear and rational thinking and a structure for constructive dialogue" (18).

VI. Ethical justification

We have earlier defined risk-benefit evaluation as the process of comparing risks and benefits against the given criteria to determine the significance of the risks and the benefits. The discussion on what attributes or criteria must be present, what the weights of these attributes are, what the *u* values are and why these values are so, and what the total utility values are enables for benefit-risk evaluation to take place. Benefits and risks are compared against the criteria and the values defined by the REC members, which ultimately provides a picture of why the risks are acceptable or not acceptable, and hence an evaluation of the significance of risks and benefits, through the total utility value. At the very least, pointing out these sources of evaluatory and ideological conflict and/or similarities is important information for a REC.

Ethical justification refers to the process of establishing a position by presenting sufficient grounds for it (35). Using a coherentist version of justification, this would mean the "reflective testing of our moral beliefs, moral principles, theoretical postulates, and other relevant moral beliefs to make them as coherent as possible" (35). In the Normative Empirical Reflective Equilibrium model, coherentist justification necessitates including the moral intuitions of other agents (apart from the thinker) and the use of empirical data as information about these intuitions (36); the task of the decision maker(s) is to make a coherent justification that passes the test of durability, transcendence and experienced perception (36). We do not have the leisure of space to go through these characteristics; suffice it to say that ethical justification necessitates making the following explicit: "intuitions, moral beliefs and principles, the wisdom of experienced agents, and empirical data." Only once these are made explicit could the weighing or the justificatory process ensue.

Decision theory, as we have seen above, enables risk-benefit evaluation to make these aspects explicit. "Intuitions" as judgments made directly without looking for reasons do not remain implicit because these judgments are made explicit through the attributes, attribute values, and *u* values, all of which are determined by the decision makers, in our case, the REC members. In addition, these attributes and their values provide us a picture of the decision makers' moral criteria (i.e. their moral beliefs and principles) and how much each criterion weighs. "Empirical data" is used to set the *u* values, because these values combine known facts and subjective preferences. Lastly, all of these are reflective of the "wisdom of experienced agents." In doing so, decision theory, when used in risk-benefit evaluation, truly becomes

useful in the process of ethical justification, and hence, in the decision making task of RECs. Such an explicit and systematic discussion should aid in addressing the problem we stated earlier in this chapter (i.e., how can RECs balance risks and benefits?). It also addresses some of the problems posed by van Luijn et al. earlier, such as the problems on the criteria and the systematization of the risk-benefit evaluation.

VII. Limitations of decision theory

Of course, just like any model, decision theory is limited by its assumptions. First, the assumption of the principles of consistency limits RECs from making eccentric intuitive evaluations (i.e. evaluations that do not logically jive with the *u* values and the weights). Consistency demands the checking of the coherence of the values and weights, and deviations from this coherence is assumed to be irrational until the decision maker can reasonably defend and provide a reasonable value to this deviation.

In terms of costs, at least for the purposes of RECs, MAUT or decision theory in general would not be demanding in terms of information technology software; a simple spreadsheet software may be sufficient. However, RECs would need some hours of training.

Lastly, not all biases that could affect intuitions may be addressed by a decision theory method. Within the risk literature, feelings may be categorized as integral to the risk issue or incidental to it (37). Integral feelings may be made explicit by the attributes, weights, and others; whereas incidental feelings, such as the positive feelings one may have on a sunny day, are more difficult to address. These sort of biases and incidental feelings are currently receiving much attention within risk studies (37, 38). How such biases could affect REC members is an area for future study.

VIII. Concluding remarks

The assessment of risks and benefits of a clinical trial is the responsibility of the sponsor, the investigator, and the REC. In this article, we limited ourselves to the risk-benefit evaluation task of RECs. We argue that decision theory, specifically through EUT and MAUT, could help make risk-benefit evaluation as explicit as possible. Not only are probabilities and best available facts made explicit; personal values, moral principles, intuitions, and expert opinion are all made explicit through utility values, attribute weights, and total utility scores. Making these explicit through the decision theory framework enables for a better-informed ethical justification process, and thus, a more rationally defensible decision making process.

In this article, we have merely presented how decision theory could aid in risk-benefit evaluation. Admittedly, there are still some loose ends like when is EUT preferable over MAUT (or vice versa) or what the best means to use in assigning *u* values. There may also be issues over whether subjective or objective probabilities are used. These are issues for further research. At this point, it is first necessary to point out that decision theory, because it is increasingly being used in drug regulation, is also useful when determining the ethical acceptability of a drug trial.

Reference List

(1) National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (US). The Belmont Report. 1979 Apr 18.
(2) World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. 2008.
(3) Council for International Organizations of Medical Sciences. International ethical guidelines for biomedical research involving human subjects. 2002.
(4) World Health Organization. Operational guidelines for ethics committees that review biomedical research. World Health Organization 2000.
(5) European Parliament. Directive 2001/20/EC on the approximation of the laws, regulations and administrative provisions of the Member States relating to the implementation of good clinical practice in the conduct of clinical trials on medicinal products for human use. 2001.
(6) King NM, Churchill LR. Assessing and comparing potential benefits and risks of harm. In: Emanuel E, Grady C, Crouch RA, Lie RA, Miller FG, Wendler D, editors. The Oxford textbook of clinical research ethics.New York: Oxford University Press; 2008. p. 514-26.
(7) Van Luijn HE, Musschenga AW, Keus RB, Aaronson NK. Evaluating the risks and benefits of phase II and III cancer clinical trials: a look at Institutional Review Board members in the Netherlands. IRB 2007 January;29(1):13-8.
(8) Van Luijn HE, Musschenga AW, Keus RB, Robinson WM, Aaronson NK. Assessment of the risk/benefit ratio of phase II cancer clinical trials by Institutional Review Board (IRB) members. Ann Oncol 2002 August;13(8):1307-13.
(9) Van Luijn HE, Aaronson NK, Keus RB, Musschenga AW. The evaluation of the risks and benefits of phase II cancer clinical trials by institutional review board (IRB) members: a case study. J Med Ethics 2006 March;32(3):170-6.
(10) Westra A, de Beaufort I. The merits of procedure-level risk-benefit assessment. IRB 2011. 33:7-13.
(11) Bernabe RD, van Thiel GJ, Raaijmakers JA, van Delden JJ. The risk-benefit task of research ethics committees: an evaluation of current approaches and the need to incorporate decision studies methods. BMC Med Ethics 2012;13:6.
(12) Weijer C, Miller PB. When are research risks reasonable in relation to anticipated benefits? Nat Med 2004 June;10(6):570-3.
(13) Miller P, Weijer C. Evaluating benefits and harms in clinical research. In: Ashcroft RE, Dawson A, Draper H, McMillan JR, editors. Principles of Health Care Ethics, Second Edition. Wiley & Sons; 2007.
(14) Baron J. Thinking and deciding. 4th ed. Cambridge; 2008.
(15) Wendler D, Miller FG. Assessing research risks systematically: the net risks test. J Med Ethics 2007 August;33(8):481-6.

(16) European Medicines Agency. Benefit-risk methodology project: Work package 1 report: Description of the current practice of benefit-risk assessment for centralised procedure products in the European Union regulatory network. 2011.
(17) European Medicines Agency. Benefit-risk methodology project: Work package 2 report: Applicability of current tools and processes for regulatory benefit-risk assessment. 2010.
(18) European Medicines Agency. Benefit-risk methodology project: Work package 3 report: Field tests. 2011.
(19) Salo A, Hamalainen RP. Multicriteria decision analysis in group decision processes. In: Kilgour DM, Eden C, editors. Handbook of Group Decision and Negotiation. Springer; 2010. p. 269-83.
(20) Reagan-Cirincione P. Improving the accuracy of group judgment; a process intervetion combining group facilitation, social judgment analysis, and information technology. Organizational Behavior and Human Decision Processes 1994;58:246-70.
(21) Matsatsinis NF, Samaras AP. MCDA and preference disaggregation in group decision support systems. European Journal of Operational Research 2001;130:414-29.
(22) The European Medicines Agency road map to 2015: the agency's contribution to science, medicine, health (draft for public consutation), 2010.
(23) Resnik M. Choices: an introduction to decision theory. Minnesota: University of Minnesota; 1987.
(24) Hansson SO. Decision theory: a brief introduction. Stockholm: Royal Institute of Technology; 2005.
(25) Baron J. Against bioethics. MIT Press; 2006.
(26) Aven T. Risk analysis: Assessing uncertainties beyond expected values and probabilities. Chicester: Wiley; 2008.
(27) European Medicines Agency -- Committee for Medicinal Products for Human Use. Reflection paper on benefit-risk assessment methods in the context of the evaluation of marketing authorization applications of medicinal products for human use. 2008.
(28) Shrader-Frechette K. Risk and rationality: philosophical foundations for populist reforms. Berkeley, Los Angeles, Oxford: University of California; 1991.
(29) Rid A, Wendler D. A framework for risk-benefit evaluations in biomedical research. Kennedy Inst Ethics J 2011;21(2):141-79.
(30) Rajczi A. Making risk-benefit assessments of medical research protocols. Journal of Law, Medicine & Ethics 2004;32:338-48.
(31) Chang R. Incommensurability (and incomparability). International Encyclopedia of Ethics. Blackwell; 2009.
(32) van der GR, van Delden JJ. Equipoise should be amended, not abandoned. Clin Trials 2011 August;8(4):408-16.
(33) Hunink M, Glasziou P, Siegel J, Weeks J, Pliskin J, Elstein A et al. Decision making in health and medicine. Cambridge University; 2001.
(34) Department of Health and Human Services (US). Federal policy for the protection of human subjects. 1991.
(35) Beauchamp T, Childress J. Principles of biomedical ethics. 6th ed. New York: Oxford University; 2008.
(36) van Thiel GJ, van Delden JJ. The justificatory power of moral experience. J Med Ethics 2009 April;35(4):234-7.
(37) Finucane M. The role of feelings in perceived risk. In: Roeser S, Hillerbrand R, Sandin P, Peterson M, editors. Handbook of risk theory. Springer; 2012. p. 677-91.
(38) Finucane M, Slovic P, Mertz C, Flynn J, Satterfield T. Gender, race, and perceived risk: the 'white male' effect. Health, Risk & Society 2000;2(2):159-72.

PART III:

THERAPEUTIC ORIENTATION IN PHASE IV

Chapter 8

PHASE IV NON-INFERIORITY TRIALS AND ADDITIONAL CLAIMS OF BENEFIT

RDLC Bernabe, G Wangge*, MJ Knol, OH Klungel, JJM van Delden, A de Boer, AW Hoes, JAM Raaijmakers, GJMW van Thiel. Phase IV non-inferiority trials and additional claims of benefit. Submitted.*

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Abstract

Non-inferiority (NI) trials in drug research are used to demonstrate that a new treatment is not less effective than an active comparator. Since phase IV trials typically aim at informing a clinical decision, the value of a phase IV non-inferiority trial hinges also on its clinical relevance. In such trials, clinical relevance would refer to the added benefit claims of a specific drug, apart from efficacy, relative to its comparator drug in the trial. In this study, we reviewed 41 phase IV trials and extracted information on whether the authors mentioned any additional benefit beyond the NI (efficacy) claim of the drug and whether the additional benefit was proven in the trial. We checked whether the additional claim was based on descriptions only or on formal statistical analyses. Our results showed that 22 out of the 41 NI trials mentioned additional benefit of the test drug and most of these claims were related to the safety profile. Of all the post-authorization NI trials that claimed additional benefit, 10 out of 22 NI trials used formal statistical analyses to show additional benefit, and only one included a sample size calculation for the additional benefit prior to the trial. We conclude that there is room for improvement in terms of designing phase IV NI trials with added benefit claims and in proving these additional claims.

I. Introduction

Non-inferiority (NI) trials in drug research are used to demonstrate that a new treatment is not less *effective* than an active comparator (1;2). Thus, an NI trial, which is mostly defined according to efficacy parameters, indirectly shows that the new treatment is also effective. However, the clinical significance of phase IV (i.e., "studies, other than routine surveillance, performed after drug approval and related to the approved indication" (3)) NI trials do not solely pertain to efficacy endpoints that were already established in pre-authorization trials. Rather, phase IV trials aim at "informing a decision" (4), or in ethics, such a trial should disturb equipoise, i.e., the "state of indifference or disagreement in the expert medical community about the net preferred medically established procedure" (5). As such, in principle, all NI trials should have additional benefit claims. Consequently, NI trials performed after authorization have a reinforced obligation to make additional claims, apart from the primary (effectiveness) endpoint, for the results of such trials to be clinically relevant. Such additional claims may relate to improved safety, but also optimization of the method of administration, improved compliance, and cost-effectiveness. Since the value of late stage NI trials depends on these additional claims, appropriate study design and/or tests to demonstrate scientific validity of such claims is truly important. Whether and how these claims are scientifically justified in the NI trials currently performed is, however, unknown.

In this study, we reviewed 41 published post-authorization NI trials and determined whether these trials reported benefit claims beyond clinical efficacy and how these additional claims were supported or proven in the trials.

II. Methods

We included all post-authorization NI trial publications among the 232 publications used for an earlier review on NI trials (6). In that review, we performed a search in PUBMED using the search terms, "non-inferior*", "noninferior*" or "active control and "equivalence", in combination with the MeSH term "humans" and "Randomized Controlled Trial" as publication type. This search resulted in 669 articles and, based on pragmatic consideration rather than formal sample size calculations, we randomly selected 300 for our review. Subsequently, we excluded studies on bioequivalence, phase I studies, non-drugs trials, and articles that did not have full-text in English which resulted in 227 articles that reported 232 NI trials.

We extracted the phase of the trial according to statements in the publications or the referred clinical-trial database (e.g. clinicaltrials.gov). We could only identify the phase of 91 NI trials. Of the 91 trials, 15 were phase IV trials. For the remaining 141 NI trials, we compared the start date of the trial with the marketing approval date of the

studied drug. The marketing approval dates were obtained from public domains. The first date of the marketing approval anywhere in the world was considered as the date of the drug's approval. If the trial started later than the drug's worldwide marketing approval date, we considered it a phase IV trial. Of these 141 NI trials, we identified 35 post-authorization trials. Hence, in total we found 50 post-authorization trials. We excluded trials that were aiming for the registration of a new indication (i.e., phase IIIB trials) by checking the aim of the trials stated in the article and by double-checking in the public domain via FDA and EMA websites. In total, we excluded nine phase IIIB trials. In the end, we included 41 phase IV NI trials in our analysis.

From each article, we extracted information on the type of drug, type of trial initiator, number of trial subjects, and the conclusion of the trial. We categorized the trials either as pharmaceutical-industry-initiated or non-pharmaceutical-industry-initiated. A trial is initiated by a pharmaceutical industry if besides the sponsoring there was active involvement of the pharmaceutical industry in the trial process. This involvement included any inputs of the pharmaceutical industry in writing the trial protocol, trial monitoring, data analysis, and reporting. If it is stated in the article that the pharmaceutical industry only gave unrestricted funding or grant, without any other involvement, we classified the trial as non-pharmaceutical industry-initiated.

Furthermore, we extracted information on whether the authors mentioned any additional benefit beyond the NI claim of the drug and whether the additional benefit was substantiated in the trial via descriptions (e.g., via simple distribution tables) or formal statistical analyses. For example, if the author mentioned that the additional benefit of the new drug was its better safety profile, we evaluated whether the safety data were presented descriptively, or if any formal testing to establish statistical significance was used to test the difference in safety profile between the two drugs. In addition, we determined whether sample size calculations for additional benefit (if any) were present and extracted the authors' conclusion on the additional benefit.

GW and RB extracted all data and, in case of discrepancies, reached consensus by discussion. All statistical analyses were performed using SPSS 19 (SPSS Inc, USA; www.spss.com).

III. Results

A. Description of the trials

Cardiovascular drugs and anti-infective drugs were the most frequently studied drugs (22 % for each; Table 1). The majority of all the trials were initiated by the pharmaceutical industry (61 %). In 73 % of the NI trials, the tested drugs were concluded to be non-inferior to their comparators.

	N(%) (unless stated otherwise)
I. Type of Drugs	
Anti-infective	9 (22)
Cardiovascular system	9 (22)
Systemic hormonal preparations	5 (12)
Vaccines	5 (12)
Musculo-skeletal system	2 (5)
Nervous system	3 (7)
Antineoplastic	2 (5)
Others	6 (15)
II. Type of trial initiators	
Non-pharmaceutical industry	12 (29)
Pharmaceutical industry	25 (61)
Not clear	4 (10)
III. Number of trial subjects (median [interquartile range])	316 (196 -629)
IV. Conclusion of the trial	
Non-inferiority	30 (73)
Superiority	2 (5)
Inferiority	6 (15)
Others	3 (7)
V. Mentioned additional benefit	22 (54)

Table 1: Characteristics of the NI trials

B. Additional benefit

Of the 41 NI trials, 22 (54 %) mentioned additional benefit of the test drug (Table 2). Among those 22 trials, the additional benefit of "better safety profile" was most often claimed (12 trials; 55 %). Twelve trials (55 %) stated that the claimed additional benefits of the test drug were proven in the current trial. In 10 trials (45%), formal tests were used to explore statistical significance of the claimed additional benefit, but only one performed a sample size calculation for the claimed additional benefit prior to the start of the trial (7).

Additional benefit (N=22)	N	Presentation of additional benefit		Conclusion on additional benefit		
		Statistical test	Descriptively	Proven	Not proven	Not explicitly discussed
Convenient method of administration	1	0	0	0	0	1
Better safety profile	12	5	7	7	3	2
Better compliance	3	1	2	3	0	0
Less costly	1	0	1	0	0	1
Convenient method of administration and better safety profile	5	4	1	2	2	1

Table 2: Characteristics of additional benefit claims

Of the 25 NI trials with pharmaceutical industry involvement, 14 (56 %) mentioned additional benefit of the test drug, while among the 12 non-pharmaceutical industry initiated NI trials, five (42 %) mentioned additional benefit of the test drug (Table 3). Fourteen of the 25 NI trials with industry involvement claimed several types of additional benefit; in five of these, statistical testing was performed, while eight simply discussed the additional benefit claims, and one did not discuss the additional benefit claim at all. For the five non-pharmaceutical industry initiated NI trials that claimed additional benefit, “better safety profile” was most often claimed (four trials). Four of the five latter trials used statistical tests to explore the additional benefit claim.

Type of initiators	Additional benefit (% type of sponsor)						
	Not mentioned	Convenient method of administration	Better safety profile	Better compliance	Less costly	Convenient method of administration and better safety profile	Convenient method of administration, better safety profile, better resistance profile
Non-pharmaceutical industry (n=12)	7 (59)	0	4 (33)	0	0	0	1 (8)
Pharmaceutical industry (n = 25)	11 (44)	1 (4)	8 (32)	1 (4)	1 (4)	3(12)	0
Not clear (n = 4)	1(25)	0	0	2 (50)	0	1 (25)	0

Table 3: Additional benefit claims based on types of sponsor

IV. Discussion

In our study of 41 phase IV NI trials, 54% reported beneficial claims in addition to the NI claim and 55% of these claims were related to safety profile. Of all post-authorization NI trials that claimed additional benefit, 45% performed tests to show statistical significance, and only one included a pre-study sample size calculation for the additional claim.

In the introduction, we stated that a post-authorization trial should aim at "informing a clinical decision." We defined "informing a decision" to refer to clinically relevant differences that would allow physicians to reasonably choose one drug over another. As such, we have hinged our definition on the obligation of the physician to choose the best-suited therapy given the patient's condition. However, these clinically relevant differences also matter in the decision-making processes of the

other stakeholders such as the regulators, patient groups, pharmaceutical industry, and third party payers. The importance of these clinically relevant differences is illustrated by the emergence of relative effectiveness as an important issue in the post-authorization stage, especially for third party payers such as the health insurance agencies (4). The European Commission's High Level Pharmaceutical Forum defines relative effectiveness as "the extent to which an intervention does more good than harm compared to one or more intervention alternatives for achieving the desired results when provided under the usual circumstances of health care practice" (4;8). Ultimately, the aim of relative effectiveness assessment is "to compare healthcare interventions in practice in order to classify them according to their practical therapeutic value" (8). We can expect this issue to sharpen as drug registration moves towards a "live license approach," i.e., an approach where launch is limited, and the widening of the scope of the license depends on post-authorization trial results (9). In the latter case, relative effectiveness matters not only for the payers but also for the regulators. Clearly, pharmaceutical companies would need to demonstrate more than ever the added value of a new drug, or in our terms, they need to demonstrate clinically relevant differences.

Our results demonstrate that this need to establish clinically relevant differences in post-authorization NI trials through added benefit claims remains to be met. The issue is emphasized by the fact that among those that made additional benefit claims, only half used formal testing to establish statistical significance, and the other half merely presented their claims descriptively. It is questionable if it is acceptable to base decisions/judgments of clinical relevance if claims are not sufficiently supported by evidence, such as those trials that only provide descriptions of the additional benefit claims. Some may argue that some additional benefits, such as the convenience of an oral route of administration compared to that of the intravenous route, may be obvious; hence, there is no need for evidentiary support. However, even for such claims, evidence is needed, as patients' preferences may be different. Oral route might be more convenient in the physician's perspective, but for the patient, the shape or the taste of the pill may be real issues, and therefore, the intravenous route could be better.

Apart from these scientific and regulatory issues with post-authorization NI trials without added benefit claims, or those with added benefit claims but without (or with questionable) scientific evidence, there is also an issue with the ethical justification of these trials. It is ethical for a trial to begin with the assumption of equipoise with the aim of disturbing it. Equipoise justifies the inclusion of patient-participants since the state of equipoise retains the possibility of a medically endorsable therapeutic benefit. Disturbing equipoise unambiguously establishes the value of an intervention, and hence, a trial that aims to disturb equipoise also aims to "improve preventive,

diagnostic and therapeutic interventions (methods, procedures, and treatments)"(10). A trial that does not show that intervention A is in some way better than intervention B does not contribute to the improvement of therapeutic interventions. Hence, a phase IV NI trial that does not aim to assess benefit claims of the new drug does not disturb nor is it expected to disturb equipoise precisely because its goal is simply to show that A is not worse than B, and not that A is in some way better than B, a goal that does not even partly resolve the state of indifference and/or disagreement in the expert medical community. As such, a phase IV NI trial without added benefit claims may have ethical justification issues. In our study, only half of the NI trials claimed such additional benefits.

Of the 25 pharmaceutical industry-initiated trials, about half (56%) claimed multiple additional benefits. The variety of additional benefit claims made by the industry seems encouraging, as this may be a sign of how the industry tries to resolve the relative effectiveness obstacle. However, the absence of statistical testing and the reliance on mere descriptions of the alleged benefit in majority of the pharmaceutical industry-initiated post-authorization NI trials bring us back to the evidence-problem we discussed earlier.

Lastly, the limited (in terms of number and variety) additional benefit claims in NI trials from independent investigators and in government initiated trials may be an indication that non-industry bodies are still generally more concerned about the narrower concepts of safety and effectiveness (as opposed to the wider benefit-risk assessment, which includes factors beyond safety and efficacy (11)). This is understandable and useful for regulatory purposes; but this situation does not help ease the impending relative efficacy and live license hurdles.

Based on the foregoing discussions, it is clear at this point that post-authorization NI trials need to be designed such that potentially, the resulting data are capable of disturbing equipoise and hence address issues such as relative effectiveness. This may be enhanced by closer and earlier collaboration between stakeholders (12;13).

Our small sample size is a limitation of this study. In addition, clinical relevance cannot be directly investigated using our data, and as such, further research is needed.

Our study clearly shows that post-marketing NI trials vary considerably in their aims and claims. Importantly, only about half of the trials claimed additional benefit. Consequently, post-authorization NI trials need to be more robust, i.e., these trials must produce information that is directly useful to the clinical setting. Moreover, these trials must show scientific validity if they are to claim any additional value that physicians can bank on. Hence, there is room for improvement in terms of designing phase IV NI trials with additional benefit claims and in proving these additional claims.

Reference List

(1) European Medicines Agency CfMPfHU. Guideline on the choice of the non-inferiority margin. 2006.

(2) US Department of Health and Human Services FaDA. Guidance for industry: non-inferiority clinical trials. 2010.

(3) General considerations for clinical trials E8, International Conference on Harmonisation, 1997.

(4) Eichler HG, Bloechl-Daum B, Abadie E, Barnett D, Konig F, Pearson S. Relative efficacy of drugs: an emerging issue between regulatory agencies and third-party payers. Nat Rev Drug Discov 2010 April;9(4):277-91.

(5) van der GR, van Delden JJ. Equipoise should be amended, not abandoned. Clin Trials 2011 August;8(4):408-16.

(6) Wangge G, Klungel OH, Roes KC, de BA, Hoes AW, Knol MJ. Interpretation and inference in noninferiority randomized controlled trials in drug research. Clin Pharmacol Ther 2010 September;88(3):420-3.

(7) Marano N, Plikaytis BD, Martin SW, Rose C, Semenova VA, Martin SK et al. Effects of a reduced dose schedule and intramuscular administration of anthrax vaccine adsorbed on immunogenicity and safety at 7 months: a randomized trial. JAMA 2008 October 1;300(13):1532-43.

(8) European Commission. Core priniciples on relative effectiveness. 2008.

(9) PriceWaterhouseCooper. Pharma 2020 the vision: which path will you take? 2007.

(10) World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. 2008.

(11) Breckenridge A. The big society and the regulation of medicines. Feb 12, 2011.

(12) Eichler HG, Pignatti F, Flamion B, Leufkens H, Breckenridge A. Balancing early market access to new drugs with the need for benefit/risk data: a mounting dilemma. Nat Rev Drug Discov 2008 October;7(10):818-26.

(13) CMR International Institute for Regulatory Science. New development paradigms: building regulatory confidence for the early release of medicines. 2010 Nov 10; London 2011.

Chapter 9

THE FIDUCIARY OBLIGATION OF THE PHYSICIAN-RESEARCHER IN PHASE IV TRIALS

RD Bernabe, GJ van Thiel, JA Raaijmakers, JJ van Delden. The fiduciary obligation of the physician-researcher in phase IV trials. Submitted.

Abstract

In this chapter, we argue that within the context of phase IV, physician-researchers retain their fiduciary obligation to treat the patient-participants. We do so by first clarifying why the perspective that research ethics ought to be differentiated from clinical ethics is not applicable in phase IV, and therefore, why therapeutic orientation is most convivial in this phase. Next, assuming that ethics guidelines may be representative of common morality, we showed that ethics guidelines see physician-researchers as primarily physicians and only secondarily researchers. We then elaborated on what a fiduciary obligation is and how some of the obligations are default duties. Lastly, assuming the entwinement of research and practice in phase IV, we showed that physician-researchers, in collaboration with other researchers, investigators, and research ethics committees, should ensure that in terms of study design, methodology, and research practice, the therapeutic value of the research to the patient-participants is not diminished.

I. Introduction

The importance of a more rigorous and scientifically fertile phase IV within the drug development system (1) is increasing both for the continuous appraisal of the benefit-risk profile of a drug and for the evaluation of the drug's economic value (for reimbursement purposes, for example). In the case of the former, the continuous appraisal of a drug's benefit-risk profile is highlighted by the present drive towards a shorter but more efficient pre-authorization drug development phase (2) and the concomitant move towards progressive authorization, i.e., authorizations that allow earlier but limited release of a drug and license expansion is dependent on new data (3). On top of that, there is increased attention on phase IV studies required by the FDA due to safety signs that may affect the benefit-risk profile of a drug (4;5).

By phase IV, we refer to "all studies (other than routine surveillance) performed after drug approval and related to the approved indication" such as "drug-drug interaction studies, dose-response or safety studies and studies designed to support use under the approved indication" (6) as well as studies to obtain health economic data. These studies are usually "larger, less technically complicated than pre-registration studies, have fewer inclusion/exclusion criteria and are more likely to include subjective or qualitative end points" (7). Also, these studies are meant to gather real-world data. As such, many or most phase IV studies occur within the doctor's clinic.

Granted the fact that not all safety and efficacy issues are known at the time of approval, it is also a given fact that upon authorization, drugs are declared to have proven safety, efficacy, and quality, and as such, it is reasonable for patients and medical practitioners to have beneficial expectations from these drugs. In a phase IV study, therapy and research are necessarily intertwined due to the tension between the reasonable expectation of benefit and the knowledge gaps in drug safety and efficacy. Social policies such as coverage with evidence development assume this entwinement by making access to therapy dependent on research participation. This entwinement is highlighted by the fact that these studies occur within the doctor's clinic, and thus the physician-researcher conflict is especially present in phase IV.

In this chapter, we shall argue that *since phase IV trials are by nature, purpose, and setting closer to practice that the other phases of drug development, physician-researchers are primarily physicians and secondarily researchers whose fiduciary obligation to their patient-participants remains, though some aspects of this obligation have been waived.* When we speak of physicians in this chapter, we refer specifically and narrowly to treating physicians and not to career researchers who happen to have a medical degree. Further, we shall limit ourselves to phase IV trials that are interventional, i.e., trials where the therapy that the patient-participant

receives is dictated by the protocol; the physician's prescription is related to the patient-participant's inclusion in the study; and additional diagnostic or monitoring procedures are necessary (8).

II. The conflict: phase IV research and therapeutic obligation

A. Two approaches on clinical research ethics dilemmas

Dilemmas in clinical research ethics are usually approached by either A.) stating that research and practice are different and hence the ethical requirements of research ought to be differentiated from the requirements of practice; or, B.) by viewing research as essentially related to practice. These two approaches are best represented by the discussion in the literature on therapeutic orientation (9-13). By therapeutic orientation, we refer to the inclination or the mindset where research is seen in terms of therapeutic morality (9), i.e., the mindset that does not fully separate or fully distinguish the following:

> ..."practice" refers to interventions that are designed solely to enhance the well-being of an individual patient or client and that have a reasonable expectation of success…. By contrast, the term "research" designates an activity designed to test an hypothesis, permit conclusions to be drawn, and thereby to develop or contribute to generalizable knowledge... (14)

F. Miller and Rosenstein (9) and Appelbaum and Lidz (15) may be representative of perspective A on the practice-research distinction. For them, the difference in research and practice in terms of aims and relationships are ethically significant: research aims to "produce generalizable knowledge" while practice aims to "provide individual patients with optimal care". Hence, therapeutic orientation ought to be seen as a problem that must be solved in research ethics. On the other hand, Anderson (16), Freedman (17), Comoretto (12), and Lemmens and P. Miller (18) represent perspective B. For Anderson, for example, research and practice are epistemologically linked since practice provides methodological constraints to research (16). In terms of therapeutic orientation, removing it from research is an approach (18) that unnaturally separates research from its goal, i.e., therapeutic benefit.

In this chapter, we relate more to perspective B and we shall do so by putting therapeutic orientation within the discussion on the fiduciary obligation of physician-researchers. But before we explicate our point, some words are in order why perspective A is simply not applicable to phase IV.

B. Why perspective A is not applicable to the physician-researcher dilemma in phase IV

Phase IV is a peculiar phase among the other phases of drug development precisely because of the marketing authorization of the drug being studied within this phase. Thus, unlike earlier phases, a comparative phase IV study refers to the comparison of two authorized drugs. Authorization means that it is logical to expect a two-armed trial between a study drug and a non-placebo comparator to have reasonable levels of safety and effectiveness. This is a noteworthy difference between phase IV and the other phases where safety and efficacy cannot yet be reasonably expected. This means that to a certain extent, any phase IV trial that excludes a placebo arm is naturally therapeutic.

In addition, since the purpose of phase IV trials is to gather real-life information, the common setting for these usually large and less technically complicated trials is the physician's clinic. This means that in terms of both goal (i.e., to get real-life data) and setting, phase IV trials are intimate with practice.

Since by nature, purpose, and setting, phase IV trials are closer to practice than the other phases, and to a certain extent are not only close but may in fact be intertwined with practice, perspective A, which demands two separate ethics for research and practice, is simply not applicable for this phase.

III. Physician-researchers are primarily physicians

Physician-researchers are primarily physicians who are engaged in research; they are not dissociative identity professionals who struggle between being fully a physician and being fully a researcher. By looking at some medical ethics guidelines for physicians, we get a better grasp of this. Admittedly, we are not *arguing* for this point; rather, we are demonstrating that based on the ethics codes of some medical associations, it is the predominant perception that physician-researchers are primarily physicians who are doing research.

The 2008 Helsinki Declaration is unambiguous in terms of the priorities of physicians involved in research (refer to Table 1). Since the Helsinki Declaration is a document that was ratified with the participation of delegates from its constituent member countries, and organizations such as the International Conference on Harmonisation (19) and the European Medicines Agency (20) have since acknowledged the authority of this declaration without issuing any divergence or disagreement with it to the present, the moral ascendancy of this declaration over its constituent member countries is almost without question (with the exception of the US FDA which disregards the current version for foreign clinical studies (21)).

Apart from the Helsinki Declaration, the Australian Medical Association's and the UK General Medical Council's codes of medical ethics provide explicit and straightforward statements on physicians' priorities when involved in research (refer to Table 1).

Medical association	Statement in the medical ethics guideline on physician priority in research
World Medical Association(22)	Declaration of Helsinki: 3. It is the duty of the physician to promote and safeguard the health of patients, including those who are involved in medical research. The physician's knowledge and conscience are dedicated to the fulfillment of this duty. 4. The Declaration of Geneva of the WMA binds the physician with the words, "*The health of my patient will be my first consideration*," and the International Code of Medical Ethics declares that, "A physician shall act in *the patient's best interest* when providing medical care." 6. In medical research involving human subjects, *the well-being of the individual research subject must take precedence* over all other interests.
Australian Medical Association(23)	AMA Code of Ethics: 1.2 Clinical Research c. Recognise that considerations relating to *the well-being of individual participants in research take precedence* over the interests of science or society.
UK General Medical Council(24)	Good Medical Practice (Research): 71. If you are involved in designing, organising or carrying out research, you must: a. *put the protection of the participants' interests first*

Table 1: Ethical codes of some medical associations that state what the priority is of the physician-researcher when doing research

What do we learn from these ethics codes? First, these are ethics codes for physicians who may be doing research, and hence, physician-researchers are not individuals with two contrasting and separate hats: that of the physician and that of

the researcher. Rather, they are physicians who must follow certain guidelines when involved in research. Second, these ethics codes explicitly state that in the event that a physician engages herself/himself in research, the priority is clear: the well-being/health/interest/protection of the patient-participant. Granted that there may be variations on how to interpret words like "well-being" or "interest", it is still without doubt that these various codes require the physician to put the patient first over research interests.

In the succeeding sections, we aim to provide further clarification of what it means for physicians to put the patient-participant first.

IV. The fiduciary obligation of physicians and the possibility of waiver

We wish to show that physicians are fiduciaries who waive some of their obligations during research. To do so, we shall first discuss what we mean by a fiduciary relationship; describe the physician-patient relationship as a fiduciary relationship; and discuss the possibilities of waiver of the fiduciary obligation for purposes of research.

A. Fiduciary relationships

A fiduciary relationship is a service relationship that is meant for the provision of a service that public policy encourages (25). In a fiduciary relationship, two or more persons are involved: the fiduciary, the entrustor, and in some instances, the beneficiary who may be distinct from the entrustor such as the case of trustors-trustees-beneficiaries. In most cases however, entrustors and beneficiaries are the same. Relationships such as the following are considered fiduciary: solicitor-client, director-corporation, trusee-trustor, and of course, physician-patient (25;26). A fiduciary relationship is distinct from a contractual relationship due to the power imbalance between the fiduciary and the entrustor. In a contract relation, the two contracting parties are considered as independent; in a fiduciary relationship, the fiduciary is entrusted with power to enable her/him to provide a specific service to the entrustor. Precisely because of this power and the service that the fiduciary provides through this power, the entrustor is to a certain extent necessarily dependent on the fiduciary (27).

Traditionally, the duties of the fiduciary may be categorized into two: the duty of loyalty and the duty of care. The duty of loyalty refers to the broad category of preventative duties that protect the entrustor's right to honesty, and hence, the prevention of the fiduciary from using power without authorization (25). To uphold this broad duty, fiduciaries may be required, for example, to provide a regular accounting of entrusted assets, to segregate and earmark these assets, to not

compete with the entrustor within the service area concerned, and not to create situations in which the fiduciary may have a conflict of interest that may compromise the entrustor (25).

The duty of care, on the other hand, addresses the entrustor's right to receive quality service from their fiduciaries. It is the demand that fiduciaries should provide their services with reasonable care and skill (25). Specifically, it demands fiduciaries to make good service decisions by "gathering pertinent information; focusing – pay attention—and deliberate before making a decision; and use their skills in the process" (25).

It is important to note that the degree of strictness of the fiduciary duties varies from one type of fiduciary to another and these variations depend on the type of power entrusted to them, the availability of "monitoring and controls" that entrustors have over the fiduciaries, the cost of using these monitors and controls over the fiduciaries, the gravity of the risk with which entrustors are exposed to due to the imposition of power to the fiduciary, and the lack of alternatives to protect entrustors from these risks (25). Thus, depending on these factors, the fiduciary duties of escrow agents are less strict than that of directors; and that of directors are less strict than that of trustees (25). We shall not go into the details of the strictness; it is sufficient for our purposes to state that there are variations on the strictness of fiduciary duties depending on the factors we enumerated.

B. Physician-patient relationship as fiduciary relationship

That physicians are fiduciaries to their patients is best expressed in cases such as *Norberg v. Wynrib.* In the latter case, for example, the Canadian Supreme Court unequivocally characterized physician-patient relationship as *fundamentally* fiduciary in nature (28). As fiduciaries, without discounting the patients' right and capacity for self-determination, physicians have duties of loyalty and care towards their patients. In terms of the duty of loyalty, the demands of which we have outlined above, in compliance with their duty to account for "entrusted assets", physicians are required to protect the patient's privacy by for example safeguarding the patient's information. They should also not directly market and sell drugs to their patients, as this puts them in direct conflict of interest with their patients. Engaging in "inappropriate sexual relationship or committing sexual misconduct" (29) is another example where physicians breach their duty of not letting their personal interest conflict with their patients (30). The breach of the duty of loyalty in all of these cases exemplifies abuse of the power vested on the physician. We shall see in a short while that though engaging in research also qualify as a conflict of interest, there are procedures that allow for the waiving of the duty to not engage in activities that conflict with the patients' best interest.

The duty of care, on the other hand, refers to the duty of physicians to "exercise reasonable care, diligence and skill in the exercise of their discretionary power (e.g., clinical judgment in the diagnosis and treatment of a patient)" (30). This may refer, for example, to physicians following GCP protocols, requesting the necessary diagnostic tests before providing a diagnosis, engaging the patient in the treatment through shared decision making and personalized care, providing balanced treatment options and recommendations based on the patient's individualized condition, providing treatment follow-ups, among others.

C. Possibilities of waiver of some of the fiduciary obligations for purposes of research

In some instances, fiduciary duties may be considered as default rules, i.e., rules that "apply unless otherwise agreed" (31). Default rules may be waived through some sort of agreement and procedure.

According to Frankel, *most* fiduciary obligations are default obligations (32). As such, it is possible for some fiduciary obligations not only to be waived, but also to be replaced by a contract, i.e., fiduciaries may propose to their beneficiaries that some of their responsibilities be waived and contracted. However, due to the dependence of entrustors on beneficiaries, waiving may only be possible if the following procedures are followed:

> Fiduciaries must put entrustors on notice that, regarding the specified transaction, entrustors are on their own; entrustors must have legal capacity to enter into bargains with their fiduciaries as independent parties; to enable entrustors to make informed decisions, fiduciaries must provide them with information regarding the transaction… (25)

The above-mentioned procedure is exactly the principle behind informed consent in research: patients are informed, and hence put on notice, that once they sign the form, certain obligations of the physicians are waived or compromised due to research; in the process of obtaining informed consent, the patient's capacity to consent must be ascertained; lastly, in informing the patient about the research, information sheets (or other similar materials) are provided and explained to make sure that all the necessary research procedures and repercussions are explained.

In the literature, there are discussions on whether the physician-researcher has fiduciary obligations to patient-participants (33-35). We think the literature has contributed greatly in expounding on the negative and positive obligations of researchers towards research participants. *However, at least for physician-researchers and based on the foregoing discussion, we think it is unnecessary to labor*

whether she/he, as a researcher, has a fiduciary obligation towards the patient-participant. It makes much more sense to view the physician-researcher as someone whose primary fiduciary obligation is to take care of the well-being of the patient, but in instances of research, she/he waives some of these obligations through the informed consent procedure.

In research, some obligations are waived such as the obligation towards personalized care, or the obligation of loyalty not to conflict with the patient's best interest. The patient-participant is placed in a situation where treatment will be based on the protocol and not only on the evaluation of the patient's individualized condition. However, as a natural fiduciary, the physician-researcher retains her/his unwaived obligations such as the obligation to deliberate on the patient's situation, and hence, decide whether it is still reasonable for the patient to be part of the trial or whether, for the patient's interest, the patient ought to the removed from the trial. Or, in the event that the physician-researcher is involved in the design of the trial, she/he must "put the protection of the participants' interests first" (24) by making sure that proper safety procedures are present and that risks are acceptable to the patient-participants. Indeed, Helsinki art.11 lists the physicians' (fiduciary) duties that are retained in a trial: "It is the duty of physicians who participate in medical research to protect the life, health, dignity, integrity, right to self-determination, privacy, and confidentiality of personal information of research subjects."

Hence, not all fiduciary duties are default duties. Frankel mentions three instances when fiduciary obligations are mandatory: when leveling the playing field for fiduciaries; when protecting the fundamental tenets of society; and when providing paternalistic protections (32). It will be best to briefly illustrate how some of the restrictions in ethics guidelines may be rooted or contextualized within these mandatory fiduciary obligations.

Leveling the Playing Field. The retained obligations in Helsinki 11 as we saw above provide for a level playing field. These retained obligations ensure that the quality of services is not "less-than-acceptable" (32) in *all* clinical trials. Thus, the field is not only more or less level for patient-participants but for the physician-researchers as fiduciaries as well.

Protecting Society's Fundamental Tenets. A physician may also not engage her/himself in a research with unacceptably high risks or with research that is methodologically faulty because researches such as these go against the fundamental tenet of society of protecting its citizens against undue harm. As somewhat an articulation of a prohibition on physicians from involving themselves in trials with unacceptable risk, Helsinki 22 states the following: "Physicians may not participate in a research study involving human subjects unless they are confident that the risks involved have been adequately assessed and can be satisfactorily managed." In the

same manner, Helsinki 12 also stipulates that a trial must in all instances be scientifically sound; as such, physicians may not engage themselves in researches that are methodologically faulty or are only scantly scientific but are cover-ups for other purposes such as marketing and promotion.

Providing Paternalistic Protections. In instances of patient-participant incompetence, paternalistic protections require physician-researchers, for example, to deal with both the patient-participant's legally authorized representative and the patient-participant and to clearly explain to them which aspects of "care are related to the research" (Helsinki 34). Having to deal with legally authorized representatives, and not just the incompetent patient-participants, is mandatory.

V. The physician-researcher within the context of phase IV

We earlier saw that phase IV trials are intimately linked to practice such that the therapeutic expectation of the patient-participant is not something that needs vigorous dispelling: with the exception of placebo arms, safety and effectiveness ought to be reasonably expected; in addition, this therapeutic expectation from patient-participants, and maybe even of the physician-researchers, is part of real life, the setting from which phase IV trials aim to gather evidence from. With this in mind, and given our earlier discussion on fiduciary obligation, we can with confidence say that *within the context of post-authorization trials, physician-researchers as fiduciaries have a therapeutic obligation to their patient-participants.* Simply put, in phase IV, physician-researchers ought to be more inclined towards practice than to research (36). Hence, in this phase, on top of the generic mandatory obligations of physicians as fiduciaries, the fiduciary obligation of the physician to treat (i.e., her/his therapeutic obligation) is not easily waived as in other phases.

However, though the end-provider of this therapeutic obligation in phase IV is the physician-researcher, the responsibility of safeguarding the therapeutic aspect of phase IV cannot lie on the physician alone. Physician-researchers, investigators, and research ethics committees should all allow for the environment where this therapeutic obligation of the physician is upheld. Concretely, this may mean their cooperation to fulfill the following:

1.) the trial methodology and study design should consider the therapeutic value of the trial to the patient-participant;
2.) that as much as possible, placebo is not used;
3.) that nonblinded studies are preferred over blinded ones to allow the physician-researcher to discuss the ramifications, effects, and side-effects of the drug to the patient-participant;

4.) that as much as reasonably possible, with the exception of the trial drug, the physician-researcher should be allowed to prescribe other drugs and request necessary diagnostic tests for therapy purposes;
5.) that superiority trials are preferred over noninferiority trials due to the clinical value of the previous over the latter.

VI. Conclusion

Physicians are the fiduciaries of patients and as such, they ought to put the interest of the patient first. In some instances, the waiving of some of the obligations of the physicians to the patients is possible, as in the case of research. However, fiduciary obligations are not always default obligations. In phase IV where research is more intimately related to practice, the physician-researcher ought to lean more towards practice than to research. Hence, in this phase, the fiduciary obligation to treat is not as easily waived as in earlier trials. Concretely, this means that physician-researchers (in collaboration with other researchers, investigators, and research ethics committees) should ensure that in terms of study design, methodology, and research practice, the therapeutic value of the research to the patient-participants is not diminished.

Reference List

(1) van Thiel GJ, van Delden JJ. Phase IV research: innovation in need of ethics. J Med Ethics 2008 June;34(6):415-6.
(2) CMR International Institute for Regulatory Science. New development paradigms: building regulatory confidence for the early release of medicines. 2010.
(3) PriceWaterhouseCoopers. Pharma 2020: the vision. 2007.
(4) Mello MM, Goodman SN, Faden RR. Ethical considerations in studying drug safety--the Institute of Medicine report. N Engl J Med 2012 September 6;367(10):959-64.
(5) Committee on Ethical and Scientific Issues in Studying the Safety of Approved Drugs. Ethical and scientific issues in studying the safety of approved drugs. Institute of Medicine of the National Academies (US), 2012.
(6) General considerations for clinical trials E8, International Conference on Harmonisation, 2010.
(7) Johnson-Pratt LR. Phase IV drug development: post-marketing studies. In: Edwards LD, Fletcher AJ, Fox AW, Stonier PD, editors. Principles and Practice of Pharmaceutical Medicine. 2nd ed. John Wiley & Sons; 2007. p. 119-20.
(8) Bernabe RD, van Thiel GJ, Raaijmakers JA, van Delden JJ. Is informed consent necessary for randomized Phase IV 'observational' drug studies? Drug Discov Today 2011 September;16(17-18):751-4.
(9) Miller FG, Rosenstein DL. The therapeutic orientation to clinical trials. N Engl J Med 2003 April 3;348(14):1383-6.
(10) Jansen LA. Doctor vs. scientist? Hastings Cent Rep 2008 March;38(2):3.

(11) Orentlicher D. Making research a requirement of treatment: why we should sometimes let doctors pressure patients to participate in research. Hastings Cent Rep 2005 September;35(5):20-8.
(12) Comoretto N. Rethinking the therapeutic obligation in clinical research. In: Schildmann J, Sandow V, Rauprich O, Vollman J, editors. Human Medical Research: Ethical, Legal and Socio-Cultural Aspects.Basel: Springer; 2012. p. 55-63.
(13) Verweij MF. Commentary: the distinction between research and practice--a response to T. Beauchamp. J Intern Med 2011 April;269(4):388-91.
(14) National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (US). The Belmont Report. 1979 Apr 18.
(15) Appelbaum PS, Lidz CW. Clinical ethics versus clinical research. Am J Bioeth 2006 July;6(4):53-5.
(16) Anderson JA. Clinical research in context: reexamining the distinction between research and practice. J Med Philos 2010 February;35(1):46-63.
(17) Freedman B. Equipoise and the ethics of clinical research. N Engl J Med 1987 July 16;317(3):141-5.
(18) Lemmens T, Miller PB. Avoiding a Jekyll-and-Hyde approach to the ethics of clinical research and practice. Am J Bioeth 2002;2(2):14-7.
(19) International Conference on Harmonisation. Guideline for good clinical practice E6. 1996.
(20) European Medicines Agency. Good-clinical-practice compliance. European Medicines Agency 2012.
(21) US FDA. Acceptance of foreign clinical studies -- information sheet. US FDA 2011 August 9.
(22) World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. 2008.
(23) Australian Medical Association. AMA code of ethics. 2006.
(24) General Medical Council (UK). Good medical practice: research. UK General Medical Council 2012.
(25) Frankel T. Fiduciary duties. In: Newman P, editor. Palgrave Dictionary of Economics and the Law. 1998. p. 127-32.
(26) Litman MM. Fiduciary obligation, law of. The Canadian Encyclopedia 2012.
(27) Frankel T. Fiduciary law. California Law Review 1983;71(3):795-836.
(28) Laura Norberg v. Morris Wynrib. Norberg v. Wynrib. 18-6-1992. Court of Appeal for British Columbia.
(29) Medico-legal handbook for physicians in Canada. The Canadian Medical Protective Association 2010;(7th).
(30) Miller PB, Choudhry S, Campbell A. Legal regulation of the physician-patient relationship. Royal College of Physicians and Surgeons of Canada 2012.
(31) Barnett R. The sound of silence: default rules and contractual consent. Virginia Law Review 1992.
(32) Frankel T. Fiduciary duties as default duties. Oregon Law Review 1995;74:1209-77.
(33) Coleman C. Duties to subjects in clinical research. Vanderbilt Law Review 2005;58(2):387-449.
(34) Miller PB, Weijer C. Fiduciary obligation in clinical research. J Law Med Ethics 2006;34(2):424-40.
(35) Morreim EH. The clinical investigator as fiduciary: discarding a misguided idea. J Law Med Ethics 2005;33(3):586-98.
(36) Resnik DB. The clinical investigator-subject relationship: a contextual approach. Philos Ethics Humanit Med 2009;4:16.

Chapter 10

GENERAL DISCUSSION

Section III of the general discussion is partly based on,

RD Bernabe, GJ van Thiel, JA Raaijmakers, JJ van Delden. Phase IV Non-interventional drug studies, waiving of informed consent, and the waiving of the participants' rights. Submitted.

In the course of this thesis, we have gone through the broad issues of informed consent, risk-benefit evaluation, and therapeutic orientation within phase IV with the hope of demonstrating the complexities and the nuances that ought to be considered when ethically deliberating about phase IV research. Far from simply adopting earlier research ethics "templates", rethinking and, if needed, revisions of the applicability of ethical principles may be called for. We have attempted to do the rethinking in the previous pages. Below would be the précis, a brief situationer, and the reformulations of these thoughts on ethics in phase IV.

I. A Recapitulation

In the earlier chapters, we deliberated on the question of informed consent and waiving in three different phase IV situations. First, we demonstrated that in phase IV non-interventional studies, though informed consent remains the standard, the manner of collecting and the content of the informed consent form differ from those of the earlier phases. For one, both opt-in and opt-out procedures are ethically acceptable. Also, given the presence of a substantive justification, waiving of informed consent may be ethically acceptable in "exceptional" circumstances. We then looked at phase IV studies where the only intervention is the randomization of the participants in terms of the trial drug and the comparators while the other procedures remain "standard clinical practice". In these studies, the waiving of informed consent is not ethically defensible, though in cases of minimal risk, an opt-out procedure may be ethically defensible. Lastly, we looked at the case of collecting the informed consent of psychiatric patients for the biobanking of their blood for both clinical use and pharmacogenetic research. In the case of the latter, by considering the risks and the decisional competence of these patients, neither the waiving of informed consent nor an opt-out procedure is ethically justifiable. Instead, an enhanced opt-in procedure is necessary.

After the ethical reflection on informed consent, we then looked at the applicability of decision theory methods in the balancing of benefits and risks in clinical trials. To do so, we first raised the issue of the need for clarity and reasonableness in the balancing of risks and benefits. Next, we looked at the two prominent benefit/risk assessment methods (the procedure-level approaches) in research ethics. We concluded that the main difficulty of the methods is the difficulty of conflation and demonstrated that research ethics would benefit from incorporating decision theory methods in the various benefit and risk weighing tasks. Lastly, we focused on the benefit/risk evaluation task of research ethics committees and showed that expected utility theory, and in particular, the multiattribute utility theory, may aid in making the weighing task explicit and less intuitive.

The third part of the thesis dealt with the therapeutic orientation of phase IV. In discussing this issue, we needed first to see the status quo. Hence, given the assumptions that phase IV trials should typically aim at informing a clinical decision and that the value of a phase IV trial hinges on its clinical relevance, we looked at the current state of phase IV non-inferiority trials. We realized that though half of the post-authorization NI trials we studied reported additional benefit claims, these claims are seldom supported by sufficient data and formal testing to establish statistical significance. After demonstrating that the design of post-authorization non-inferiority studies ought to be improved in terms of ensuring clinical value and providing evidence for it, we explored the question on the fiduciary obligation of the physician researcher in phase IV interventional studies. We showed that since phase IV trials are by nature, purpose, and setting closer to practice that the other phases of drug development, physician-researchers are primarily physicians and secondarily researchers whose fiduciary obligation to their patient-participants remains, though some aspects of this obligation may have been waived.

II. Stepping Back

Recently, the 2012 CMR International Pharmaceutical R&D Factbook showed the following positive trends: increased number of new molecular entities launched in 2011, in fact the highest in 10 years (see Table 1); increased sales of pharmaceutical companies; increased number of submissions for marketing authorization; and decreased late-stage terminations (1). This surge of newly launched molecular entities -- coupled with the remaining challenges in drug development such as the unaddressed regulatory barriers, "inadequate clinical efficacy, lack of competitive differentiation, and safety concerns" (2) in late phase trials -- points towards the continued emphasis and need for robust phase IV. Since the importance of phase IV is undeniable given the present trend and the developments in the drug development paradigm, the necessity of a research ethics that has amply reflected on the nuances of phase IV cannot be more emphasized. The Institute of Medicine's *Ethical and Scientific Issues in Studying the Safety of Approved Drugs* dispenses the same message for the need of a research ethics that is applied in the postmarketing stage (3). Within phase IV, ethics is needed as a reflective tool that may aid in the balancing of risks and benefits and in the weighing and factoring in of various considerations in decision making (such as in balancing public health and access to innovative drugs) with research participant protection and rights.

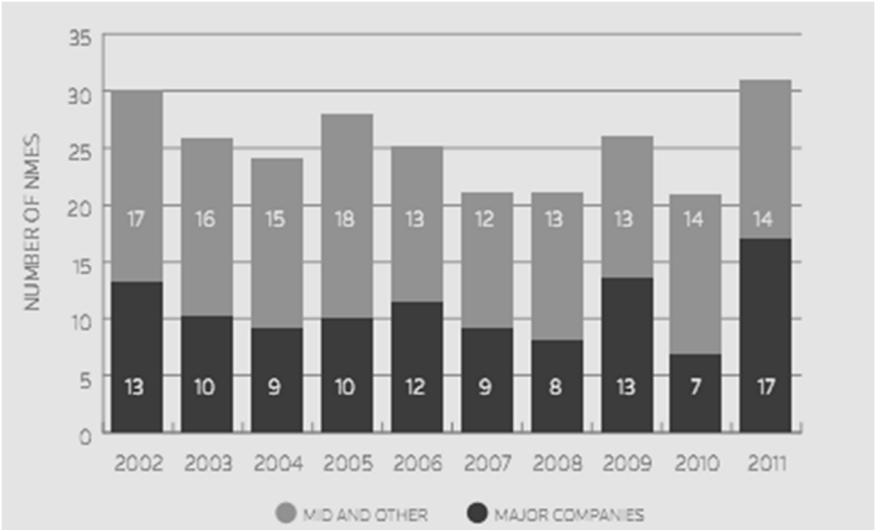

Figure 1: Number of new molecular entities first launched onto the world market by company size (1)

Given the inevitable burgeoning of robust phase IV studies and the undeniable need for research ethics that keeps up with this burgeoning, some ethical principles are indispensable.

III. Ethics in Phase IV

Throughout this thesis, we have struggled with the nuances surrounding phase IV and how ethics ought to deal with these nuances. Though this study has been limited to the issues within the protection paradigm, we can still mention a few principles when doing ethics in phase IV.

A. When discussing issues of informed consent waiver, it is ethically necessary to put such discussions within the sphere of human rights

We have seen in Chapters 2-4 that the question of the waiving of informed consent is expectedly a relevant question in phase IV, especially in non-interventional studies. The waiving of informed consent in observational studies such as epidemiological studies, though not universally applicable, is circumstantially justified by reasons such as the exposure of the participant to no more than minimal risk; the procedures to be used customarily do not require informed consent outside the research context; or when informed consent poses threat to the participant's confidentiality (3). Earlier in Chapter 3, we provided two ethical arguments that are relevant to the question and

the justification of the waiving of informed consent: the generic right argument and the harm argument. The justifications we just mentioned clearly touches on most of the aspects of the harm argument: the concept of minimal risk, for example, avoids the voluntary imposition of appreciable risks to participants' interests. However, these justifications do not explicitly touch on the generic right argument, i.e., if we may recall, that all human beings as agents have generic rights. By generic rights we refer to rights that "agents need, irrespective of what their purposes might be, in order to be able to act at all or in order to be able to act with general chances of success"(4). Even the argument that waiving may be justified when informed consent poses a threat to confidentiality is not exactly phrased as a violation of a basic human right; the term "threat" may easily be construed as to refer to exposing participants to risk, and hence, an argument that may be simplistically viewed as avoidance from harm. In what follows, we shall briefly show that the generic rights argument is indispensable if such a waiving truly may only be done in "exceptional situations".

According to the CIOMS International Ethical Guidelines for Epidemiological Studies, the "waiver of individual informed consent is to be regarded as exceptional, and must in all cases be approved by an ethical review committee"(5). If this is true, this means that deliberation on exceptionality and the weighing of factors must ensue before such a waiver is approved; a mere checklist approach is insufficient. Such a checklist approach is all the more insufficient if the list only contains the three justifications we mentioned above. These three justifications do not touch on exceptionality. At most, they add to the factors to take account of when weighing whether the waiver is justifiable. However, and more crucially, these factors do not state what is as stake, i.e., they do not touch on the very reason why such a waiver ought to be exceptional in the first place. The generic right argument provides us with this reason: such waivers ought to be granted only in exceptional situations because what is waived is the generic right of human beings to confidentiality and self-determination in terms of the use of one's (medical) records. Precisely because the issue is the waiving of human rights, a substantive justification must convincingly show that in this particular study, waiving is ethically acceptable. That in this circumstance, public health (or other concerns) weighs heavier than these rights. Hence, though the generic right argument does not provide us with the tools to weigh, it places the issue of waiving within the proper context.

B. The fact that there is a variety of phase IV trials is an ethically significant fact

The range of methodological types of phase IV studies is appreciably wide: from epidemiological studies that use a database, observational studies with subject enrolment, large simple trials with randomization, to classical randomized controlled trials (RCTs). The variety of purposes of phase IV studies account for the

methodological variety in this phase. According to the Wiley Encyclopedia of Clinical Trials, the various purposes of phase IV studies are the following: seeding; identification of rare but serious events; identification of long-term side effects; further dose investigation; to explore further indications for authorized drugs; interaction studies; comparison with other drugs; quality of life and health economics (6). Though some of these purposes may be questionable (such as that of seeding trials since the value of these trials are scientifically questionable, or the exploration of further indications since such trials may be categorized as phase IIIb trials), it is still without doubt that the variety of purposes would require various types of trial methodologies: the identification of rare but serious events may best be accomplished via large simple trials or through an observational study that utilizes a large database; the identification of long-term side effects seemingly could best be achieved through observational studies (whether via a database or with subject enrollment); further dose investigation would probably need a RCT; interaction studies may utilize observational studies and/or RCTs; drug comparison, whether non-inferiority or superiority, could best be achieved via a RCT; and quality of life and health economics studies usually utilize observational studies and/or large simple trials.

This variety in phase IV trials is ethically significant because this variety accounts for differences in terms of 1.) the demands to patient-participants and 2.) the extent of compromise on the fiduciary relationship of the physician and the patient.

1. The scale of demands on patient participation

   Depending on the type of phase IV study, the demands on patients differ: an observational study with patient enrollment may require only interviews and/or answering of questionnaires; a large simple trial may require some sort of randomization while all other interventions remain clinical and therapeutic; and an RCT would require participants to be assessed for eligibility, to be randomized, to undergo a series of tests, and to report for follow-ups. These differing demands also denote differing levels of exposure to risk/discomfort.

2. Degree of compromise in the fiduciary relationship

   As discussed in Chapter 9, physicians who involve themselves in phase IV research remain fiduciaries to their patients; however, certain responsibilities may be waived. Depending on the protocol, the responsibilities of physicians that must be waived for the sake of the trial differ: an observational study ideally should not affect the physicians'

fiduciary obligations to the patient-participants while an RCT would require certain obligations to be waived, such as the obligation to choose the best therapy based on patients' individualized conditions.

Hence, the various types of phase IV studies expose patient-participants to differing degrees of risk/discomfort and to differing degrees of compromised fiduciary obligation. Since the differing degrees of risk and compromise are by-products of the variety of types of phase IV trials, we can with confidence say that the fact that there is a variety of phase IV trials is an ethically significant fact.

C. The type differences warrant different ethical treatment on the issues of the waivability of informed consent, the manner of attaining informed consent, and the content of the informed consent form

1. Waivability of informed consent

As we saw in Chapter 2, the acceptability of a substantive justification on the waivability of the prima facie right to consent is limited to phase IV noninterventional drug studies. Once some sort of intervention or complication is present, such as that in the case of P4RODS (cf. Chapter 3), in pharmacogenetic research using non-anonymous data from psychiatric biobanks (cf. Chapter 4), in large simple trials, and of course, in RCTs, then the waiving of informed consent becomes ethically unjustifiable. We can somewhat imagine noninterventional studies with patient enrolment as the stop point and below it would be observational studies such as epidemiological studies that use databases. Beyond this stop point, informed consent is non-waivable.

2. Possibility of an opt-out system

Beyond the stop point, informed consent is non-waivable; however, this does not mean that informed consent may only be attained through an opt-in system. Depending on aspects such as decisional competence and minimal risk, an opt-out system may be ethically justifiable to accommodate research concerns such as bias and recruitment barriers. In trials where decisional competence may be questionable such as pharmacogenetic research in psychiatric biobanks, interventional trials in children, and others, an opt-out system may be ethically unjustifiable. The same may be said in trials with more than minimal risks such as RCTs.

3. Difference in the amount and kind of information in the informed consent form

Declaration of Helsinki article 24 enumerates the information that ought to be relayed to the patient-participants when seeking for their informed consent:

> In medical research involving competent human subjects, each potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, and any other relevant aspects of the study. The potential subject must be informed of the right to refuse to participate in the study or to withdraw consent to participate at any time without reprisal…(7)

In Chapter 2, we saw how the amount and kind of information that is needed in securing the informed consent of patient-participants in phase IV noninterventional studies vary from other types of trials. For example, in noninterventional studies, the understanding of risks and benefits ought not to be a great concern at least relative to interventional studies and this nuance is accounted for by the very nature of noninterventional studies: phase IV noninterventional studies ideally should not have additional risks. Hence, the informed consent form of such trials would not spend as much space on "risks/discomforts" compared to interventional studies. In this sense, the nature of a phase IV trial dictates the amount and kind of information present in the informed consent form.

Hence, trial type variability in phase IV accounts for ethically significant nuances in issues such as the waivability of informed consent, the possibility of an opt-out system, and the differences in the amount and kind of information that ought to be present in the informed consent form.

D. The ethical evaluation of a phase IV study ought to assume therapeutic orientation

Earlier in the thesis, we have showed that by nature, purpose, and setting, phase IV trials are closer to practice than the other phases. Precisely because the therapeutic orientation of phase IV stems from its very essence, any ethical reflection on phase IV is incomplete without this assumption. This therapeutic orientation is the assumption

behind our conclusion on the strength of the fiduciary obligation of physicians in phase IV; it is the same assumption behind the claim that a phase IV study, including non-inferiority trials, ought to aim for clinical significance.

E. The weighing of risks and benefits is not the sole task of the research ethics committee; rather, it is the shared responsibility of the sponsor/investigator and the research ethics committee

In any study, benefits and risks must be assessed to ensure that risks do not outweigh benefits, or simply, that risks are acceptable in relation to the objectives of the study and the study's (possible) benefits. The task of weighing benefits and risks have traditionally been vested on research ethics committees. As discussed in Chapter 6, we agree with this; indeed, it is necessary for research ethics committees to evaluate risks and benefits to ensure that patient-participants are not exposed to unnecessary and unjustified risks and to verify the scientific/social validity of a study. However, it is insufficient to put all the weighing tasks to research ethics committees. The weighing of risks and benefits ought to be cooperatively done by the sponsor and the research ethics committee: benefit/risk analysis is the task of the sponsor, benefit/risk evaluation is the task of both by the sponsor and the research ethics committee, risk treatment is the task of the research ethics committee, and decision making is also the task of the research ethics committee.

F. In the balancing of risks and benefits in phase IV, assuming therapeutic orientation and utilizing the expected utility theory (specifically the multiattribute utility theory), some ethical constraints are in order

In all the various benefit-risk tasks, decision studies methods may be helpful in making these tasks "robust, transparent, and coherent" (cf. Chapter 7). This is a conclusion that accord with the findings of the EU Benefit-Risk Methodology Project (8). Earlier in this thesis, we have shown that multiattribute utility theory, when applied to the evaluation of benefits and risks, is capable of accomplishing this claim. When applied specifically in phase IV, it is necessary to presuppose this therapeutic orientation to understand the nuances and constraints that ought to be present in the evaluation of risks and benefits. These constraints include the following:

1. The benefit utility table must necessarily include (potential) "direct benefits." By direct benefits, we refer to the benefits that patient-participants receive from the experimental intervention (9). By including direct benefits, RECs (or the sponsor) are compelled *to account for* the therapeutic value of the intervention for the patient-participants.

2. The weight of “direct benefits” cannot be negligible in comparison to the weight of other benefits, such as “benefits to society”. Admittedly, what is negligible would subjectively depend on the evaluators; nevertheless, some cases are obvious: in a scale of 1 to 10, if benefits to society weighs 8, the weight of “direct benefits” cannot be 1.

3. The risk disutility table must necessarily include the categories, “risks due to study participation” and “risks due to the experimental intervention” since these risks directly affect the therapeutic value of the trial to the patient-participants.

4. In both categories (i.e., “risks due to study participation” and “risks due to the experimental intervention”), “burdens” and “inconveniences” (whether together or separately) must be considered.

IV. Further Research

This thesis provided an initial inquiry on research ethics that is relevant in the postmarketing stage. Because of its exploratory and preliminary nature, there is yet so much to be done if research ethics is to keep up with the increasing demands of an expanding phase IV. For example, there is a need to elaborate on the following: how decision theory may aid in the other benefit-risk weighing tasks, including risk-benefit analysis and risk treatment; how therapeutic orientation may affect phase IV methodology and design; the various degrees of therapeutic orientation in the various phase IV studies; how the formulation of informed consent ought/ought not to be affected by the therapeutic orientation/fiduciary obligation; the various ways that fiduciary obligation is and may be compromised in the various phase IV studies.

In spite of the introductory nature of this thesis, it is the author’s hope that this thesis provided an impetus to nuance the discussion on ethics in phase IV.

Reference List

(1) CMR International. 2012 R&D factbook executive summary. CMR International 2012.
(2) Khanna I. Drug discovery in pharmaceutical industry: productivity challenges and trends. Drug Discov Today 2012 October;17(19-20):1088-102.
(3) Institute of Medicine. Ethical and scientific issues in studying the safety of approved drugs. Washington, D.C.: National Academies Press; 2012.
(4) Beyleveld D, Brownsword R. Consent in the law. Oxford: Hart; 2007.
(5) International ethical guidelines for epidemiological studies, Council for International Organizations of Medical Sciences, (2008).
(6) Day S. Phase IV trials. In: DÁgostino R, Sullivan L, Massaro J, editors. Wiley Encyclopedia of Clinical Trials. Wiley; 2008. p. 446-53.
(7) World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. 2008.

(8) European Medicines Agency. Benefit-risk methodology project. 2012.
(9) King NM, Churchill LR. Assessing and comparing potential benefits and risks of harm. In: Emanuel E, Grady C, Crouch RA, Lie RA, Miller FG, Wendler D, editors. The Oxford textbook of clinical research ethics.New York: Oxford University Press; 2008. p. 514-26.

Chapter 11

SUMMARY

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SUMMARY

This thesis is an attempt to raise some ethical issues that are specific to phase IV drug trials (i.e., postmarketing drug studies) and to provide preliminary responses to such issues. The issues addressed were those that fall within what van Thiel and van Delden called the protection paradigm, i.e., ethical questions that are nuanced only by the very character of phase IV and not by the various socio-economic contexts. Of course, we are by no means saying that distributive justice issues in this phase are of less importance; distributive justice issues are equally urgent and important as the problems within the protection paradigm. However, given that foundational ethical issues are conceptually prior to contextualized issues, and since this study is probably one of the first, if not the first to look at phase IV ethical issues in an extended manner, then we think it is necessary and helpful to limit ourselves to the issues within the protection paradigm. Within this paradigm, we further limited ourselves to issues of informed consent, risk-benefit assessment, and the therapeutic orientation of phase IV.

Part I: Informed consent and phase IV

Within the issue of informed consent (IC) in phase IV, we looked at three cases: that of IC in phase IV non-interventional drug studies; IC in phase IV randomized observational drug studies; and IC in psychiatric biobanks for pharmacogenetic research.

In the first case (**Chapter 2**), we looked at phase IV non-interventional drug studies (NIS). Since in the literature, there is lack of consensus on the necessity of IC for observational studies, and harmonized ethical guidelines for observational studies are wanting, we first asked if IC is necessary for these studies, i.e., if informed consent may be universally waived for all NIS. To respond to this question, we presented the three usual arguments used to waive IC in NIS: the potential benefit to society argument, risk as minimal argument, and no meaningful infringement of autonomy argument.

As to the first argument, we counterargued that it suffers from irrelevance since the argument does not touch on the very purpose of IC; instead, it goes straightaway into the benefits of waiving it. The second argument, on the other hand, touches on one of the purposes of IC, i.e., to minimize risk to the participants. However, this argument falls short of arguing for the justifiability of universally waiving IC. It is one thing to say that IC protects participants from risk and it is quite another to say that the absence of risk justifies the waving of IC. The fact that risk is minimal or absent does not lessen the participant's right to self-determination. For NIS, minimal or no risk does not give the researcher the right to enroll a participant without consent. The third argument -- which states that by alluding to the reasonable person standard, no meaningful infringement of autonomy ensues when IC is waived in NIS -- suffers from both logical and moral-rational difficulties. Logically, it fails by equating presumed consent and actual consent; moral-

rationally, it makes the whole exercise of IC depend upon the researcher's (or ethics committee's) perspective of what is reasonable and ethical, and thus defeating the very purpose of IC. Simply put, the third argument fails since the participant's generic right to autonomous decision making (and in this case, to decide to be take part or not take part in the research) is displaced by the prejudgment of the researcher/ethics committee. Hence, though there may be particular instances when IC may be waived due to acceptable substantive justifications, a universal waiving of IC in NIS cannot be argued for.

Though the universal waiving of IC in NIS cannot be argued for, it is reasonable to think that the content and manner of IC in phase IV non-interventional studies are not the same as those in other studies. In terms of content, IC in phase IV NIS would require the elaboration of the purpose of research and of the voluntary nature of the research. An explanation of the research design is also requirement; however, issues such as randomization and the benefit-risk balance are either irrelevant or are not of great importance. In terms of the manner of IC, though opt-in remains the standard, in instances when such a procedure is impracticable, an opt-out procedure may be acceptable, so long as the process remains voluntary and informative for the participants.

In the second case (**Chapter 3**), we looked at IC in phase IV randomized observational drug studies (P4RODS). In *clinicaltrials.gov*, there are phase IV studies that are registered both as randomized and observational. We realized that the question on the waiving of IC could not be properly answered unless we put into doubt the category, "randomized observational". Using the European Commission definition of an observational study, we argued that since an observational study cannot be such that therapy is dictated by the protocol, or that medical prescription has something to do with study participation, or that additional diagnostic or monitoring procedures are applied to applicant, then P4RODS is a contradiction. Hence, P4RODS ought to be P4RIDs, i.e., phase IV randomized interventional drug studies.

After establishing that P4RODS ought to be P4RIDS, we can now proceed with the question, could IC be waived? Just as universal waiving of IC in phase IV NIS cannot be ethically justified, such a universal waiving is also not justifiable for P4RIDS owing to its interventional nature. We have argued for the unjustifiability of this universal waiver of IC by using the generic right argument and Feinberg's definition of harm. Hence, the question ought to be, could circumstantial waiving of IC in P4RIDS be ethically justifiable, so long as there is substantive justification? To respond to this question, we looked at two possible circumstantial justifications for the waiving: IC in P4RIDS may be waived due to public health reasons; and that IC in P4RIDS may be waived due to the equipotent or bioequivalent nature of the drugs. That IC in P4RIDS may be waived due to public health reasons is simply not a valid argument because though nongovernmental and quasi-public institutions may be involved, for a trial to qualify officially as a public health endeavor, it ought to be led by the government. Since most P4RIDS are nongovernmental, and hence

cannot be considered public health endeavors, then public health is not the proper arena to look for a circumstantial justification. Next, we looked at drugs themselves, i.e., whether characteristics such as equipotence or bioequivalence may be possible justifications for the waiving. However, even in the absence of grave risks such as in P4RIDS on bioequivalent drugs, there might still be potential clinically relevant differences between the two drugs, and inconveniences could be expected especially in studies including modified release products. In addition, in P4RIDS, there will always be issues of conflict of interest since deviations from usual care occur due to the study. As such, we find no compelling circumstantial justification for the waiving of IC. As such, consent remains a moral necessity and IC remains the standard. However, an opt-out procedure may be warranted for low risk P4RIDS.

In the third case (**Chapter 4**), we looked at the issue of the necessity and the manner of securing the IC of psychiatric patients whose blood samples are stored in a psychiatric biobank for pharmacogenetic research. Just like the earlier cases, we began with the question, "can the waiving of IC be ethically justifiable?" For this case, we assumed that the waiving of IC may be allowed in some epidemiological research only in exceptional cases. Hence, the question of whether IC may be universally waived is already out of the picture. To investigate whether circumstantial waiving may be justifiable for this kind of research, we looked at the two often-stated conditions for waiving: risks to participants should be no more than minimal; and obtaining consent would make the research impracticable. Regarding the first condition, we argued that the status quo does not allow us to claim that risks in such biobanks are minimal; indeed, social, psychological, and economical risks may be very real risks. As for the second condition, we argued that patients in this case are not physically inaccessible, and as such, the claim of impracticability does not apply. We further argued that the cognitive vulnerability of these patients make the "impracticability" argument of secondary importance. Hence, we found no justification for any circumstantial waiving of IC for pharmacogenetic research in psychiatric biobanks. Further, since the patient-participants are vulnerable, only a supported opt-in procedure is justifiable. This means an opt-out procedure is also out of the picture.

Part II: Weighing of benefits and risks

Part II takes one step back. The evaluation of risks and benefits is an ethical requirement for any clinical study. Of course, this applies to phase IV studies as well. However, we felt there was a need to address the question, “How should evaluators do the evaluation?” before we can give any preliminary reflection on how this evaluation may be applied in phase IV. We provided some preliminary reflection on the applicability of the results of part II in phase IV in Chapter 10.

In this part, we raised the issue of the need for risk-benefit evaluation tools; evaluated current approaches and introduce how methods from decision studies may be useful in benefit-risk evaluations; and illustrated how decision studies may be useful in the benefit-risk evaluation task of research ethics committees.

In **Chapter 5**, we argued that the following predicament is artificial, "IRBs need to better evaluate the risks and benefits of a trial, but doing so would necessarily be more costly, time-consuming, cumbersome, and demanding for everyone involved since this would entail additional procedures to be standardized for the sake of ethics" (i.e., ethical inflation). We further argued that this predicament, and also therefore ethical inflation, can be avoided if we look at the issue not simply as an issue of "inflation" but an issue of clarity and transparency of what risk–benefit assessment is, and what tools may be needed to make this evaluation. Hence, briefly, we raised the issue that the evaluation of benefits and risks is not just a matter of providing (or receiving) more data. Instead, to put order in the data and to justify the demand for specific data, it is necessary to be as less intuitive and be more explicit and systematic as possible. Decision theory and risk studies were presented as possible sources of evaluation tools.

In **Chapter 6**, we evaluated the two dominant benefit-risk approaches (i.e., the procedure-level approaches): Net Risk Test and Component Analysis. The main difficulty with both approaches is the difficulty of conflation. The latter means that both approaches do not differentiate between the various benefit-risk tasks, i.e., benefit-risk analysis, benefit-risk evaluation, risk treatment, and decision making. This lack of differentiation makes both approaches susceptible to being cumbersome and confusing since the various benefit-risk tasks would have to be done by one body, the research ethics committee.

As a solution to the conflation, we resorted to risk studies and decision theory to clarify what the various tasks are; who should be responsible for the various tasks when assessing a clinical study; and how decision theory and risk studies may aid in accomplishing these tasks.

Benefit-risk analysis refers to gathering of risk and benefit events, causes, and consequences; and presenting this wealth of information in a systematic and comprehensive way, in accordance with the purpose why such information is systematized in the first place. There are various manners that analysis may be done, such as fault tree analysis, event tree analysis, Bayesian networks, Monte Carlo simulation and others. Since analysis entails presenting the wealth of data in a benefit-risk picture, we argue that the sponsor of the study ought to be responsible for it. *Benefit-risk evaluation*, on the other hand, refers to the process of comparing risk and benefit against given risk and benefit criteria to determine the significance of the risk and the benefit. The multiattribute utility theory is a possible evaluation aid. We then argued that both the sponsor and the research ethics committee ought to be responsible for this task. *Risk*

treatment refers to enhancing the trial's social value, reducing the risks to the participants, and enhancing the participants' benefits. As such, inputs from both the sponsor and the research ethics committee would be necessary for this task. Lastly, *decision making* refers to making a judgment whether, based on the foregoing, and given the benefits, the risks are acceptable in a given clinical study. This is obviously the task of the research ethics committee.

Zeroing on the benefit-risk evaluation task, **Chapter 7** demonstrated how the multiattribute utility theory may be a good tool that could aid evaluators. Using this theory, not only are probabilities and best available facts made explicit; personal values, moral principles, intuitions, and expert opinion are all made explicit through utility values, attribute weights, and total utility scores. Making these explicit through the decision theory framework enables for a better-informed ethical justification process, and thus, a more rationally defensible decision making process.

Part III: Therapeutic orientation in phase IV

Part III deals with an essential characteristic of phase IV studies, i.e., these studies' therapeutic orientation. Phase IV trials are distinct from other phases precisely because of the former's postmarketing nature. To have a better feel of the status quo, we first conducted a study to see if additional benefit claims are present in phase IV non-inferiority studies. After which, we proceeded to elaborate on the fiduciary obligation of the physician-researcher in phase IV.

Working on the assumption that the value of a phase IV trial hinges on its clinical relevance, in **Chapter 8** we reviewed 41 phase IV trials and extracted information on whether the authors mentioned any additional benefit beyond the non-inferiority (efficacy) claim of the drug and whether the additional benefit was proven in the trial. "Additional claims" may relate to improved safety, but also optimization of the method of administration, improved compliance, and cost-effectiveness. Of all the reviewed phase IV non-inferiority trials, 22 claimed additional benefit, 10 used formal statistical analyses, and only one included a sample size calculation for the additional benefit claim. Hence, we concluded that there is still room for improvement in terms of designing phase IV non-inferiority trials with added benefit claims.

In **Chapter 9**, we argued that within the context of phase IV, physician-researchers retain their fiduciary obligation to treat the patient-participants. We do so by first showing that the perspective that research ethics ought to be differentiated from clinical ethics is not applicable in phase IV. In research ethics, there is the dominant perspective that the ethics of clinical practice ought to be differentiated from the ethics of research because the goals of practice are essentially different from the goals of research. We argued that this latter argument cannot be applicable to phase IV precisely because in

phase IV, study drugs have marketing authorization. Hence, therapy is a natural expectation at this phase.

We then elaborated on what a fiduciary obligation is. A fiduciary relationship is a service relationship that is meant for the provision of a service that public policy encourages. Some fiduciary duties are waivable; however, some duties are intrinsic to the relationship. The physician-patient relationship is an example of fiduciary relationship. We argued that a physician-researcher is primarily a physician whose primary fiduciary obligation is to take care of the well-being of the patient; in instances of (phase IV) research, she/he requests the patient that some of the aspects of this obligation be waived through the IC procedure.

Lastly, assuming the entwinement of research and practice in phase IV, we showed that physician-researchers, in collaboration with other researchers, investigators, and research ethics committees, should ensure that in terms of study design, methodology, and research practice, the therapeutic value of the research to the patient-participants is not diminished.

In **Chapter 10**, we summarized the main findings of this thesis:

A. When discussing issues of IC waiver, it is ethically necessary to put such discussions within the sphere of human rights;
B. The fact that there is a variety of phase IV trials is an ethically significant fact;
C. The type differences in phase IV warrant different ethical treatment on the issues of the waivability of IC, the manner of attaining IC, and the content of the IC form;
D. The ethical evaluation of a phase IV study ought to assume therapeutic orientation;
E. The weighing of risks and benefits is the shared responsibility of the sponsor/investigator and the research ethics committee;
F. In the balancing of risks and benefits in phase IV, assuming therapeutic orientation and utilizing the expected utility theory (specifically the multiattribute utility theory), some ethical constraints are in order:
    a. The benefit utility table must necessarily include (potential) “direct benefit”;
    b. The weight of “direct benefits” cannot be negligible in comparison to the weight of other benefits, such as “benefits to society”;
    c. The risk disutility table must necessarily include the categories, “risks due to study participation” and “risks due to the experimental intervention”;
    d. In both categories (i.e., “risks due to study participation” and “risks due to the experimental intervention”), “burdens” and “inconveniences” (whether together or separately) must be considered.

SAMENVATTING

In dit proefschrift worden ethische kwesties bij fase IV geneesmiddelen onderzoek (postmarketing studies) aan de orde gesteld en er wordt een poging gedaan tot het beantwoorden van deze vragen. De kwesties die aan de orde komen vallen onder wat Van Thiel en van Delden het 'protectionistische paradigma) noemden. Het gaat om vragen die voortkomen uit de specifieke kenmerken van fase IV onderzoek, in tegenstelling tot bijvoorbeeld vragen die samenhangen met verschillende sociaaleconomische omstandigheden. Dit betekent uiteraard niet dat we willen beweren dat problemen van distributieve rechtvaardigheid in deze fase van geneesmiddelenonderzoek minder belangrijk zijn: rechtvaardigheidskwesties zijn even urgent en belangrijk als problemen die binnen het protectionistische paradigma vallen. Echter, kwesties van fundamentele aard gaan conceptueel gezien boven context-bepaalde problemen. Aangezien deze studie waarschijnlijk een van de eerste – en mogelijk zelfs de eerste – is waarin ethische kwesties in fase IV uitgebreid worden onderzocht, zijn wij van mening dat het nuttig en nodig is om onszelf te beperken tot kwesties binnen het protectionistische paradigma. Binnen dit paradigma concentreren wij ons op kwesties met betrekking tot informed consent, de verhouding tussen risico's en baten, en de therapeutische oriëntatie van fase IV.

Deel 1: Informed consent en fase IV

Ten aanzien van het informed consent (IC) in fase IV hebben we drie typen studies onderzocht: IC in non-interventie geneesmiddelenstudies; IC in fase IV gerandomiseerde observationele geneesmiddelenstudies; een IC in biobanken met materiaal van psychiatrische patienten voor farmacogenetisch onderzoek.

Het eerste type studie dat we onderzochten (**Hoofdstuk 2**), was de non-interventie geneesmiddelenstudie (NIS). Consensus over de noodzaak van IC in observationele studies zoals NIS ontbreekt in de literatuur, en eenduidige ethische richtlijnen voor dit type studies laten op zich wachten. We hebben daarom de vraag gesteld of IC noodzakelijk is voor deze studies of dat IC voor alle NIS terzijde geschoven kan worden. Onze beantwoording van deze vraag richt zich op drie veelgebruikte argumenten vóór het verlaten van de eis tot IC in NIS: het argument van de verwachte voordelen voor de samenleving als geheel; het argument van minimaal risico en het argument dat er geen sprake is van betekenisvolle inbreuk op autonomie van de proefpersoon.

Ten aanzien van het eerste argument – dat van de verwachte voordelen voor de samenleving – claimen wij dat het niet relevant is omdat het niet raakt aan het doel of de waarde van IC: het gaat alleen over de voordelen van het afzien van IC. Het tweede argument heeft dat probleem niet: het gaat in op een van de doelen van IC, namelijk het minimaliseren van de risico's voor proefpersonen. Toch schiet het argument tekort omdat het geen rechtvaardiging biedt voor het volledig opgeven van het IC vereiste. De bewering

dat IC proefpersonen beschermt tegen risico kan niet zomaar worden omgezet in de stelling dat de afwezigheid van risico's voldoende grond is voor het achterwege laten van IC. Het feit dat er geen of hooguit minimale risico's zijn doet geen afbreuk aan het recht op zelfbeschikking van proefpersonen. In het geval van NIS betekent dit dat de afwezigheid van risico de onderzoeker niet het recht geeft om een persoon in een studie op te nemen zonder diens toestemming.

Het derde argument stelt dat we ons moeten richten op het perspectief van de 'redelijke persoon', en dat daaruit volgt dat er geen sprake is van een betekenisvolle inbreuk op autonomie van proefpersonen als IC voor NIS wordt afgeschaft. Dit argument heeft zowel logische als moreel-rationele gebreken. In logisch opzicht gaat het mis door *veronderstelde* toestemming gelijk te stellen aan *werkelijke* toestemming; moreel en rationeel gezien is het niet houdbaar omdat de hele IC doctrine afhankelijk wordt van wat *redelijk* is vanuit het perspectief van de onderzoeker of de medisch-ethische toetsingscommissie. Daarmee tast dit argument de kern van IC aan. Met andere woorden: het derde argument is onhoudbaar omdat het impliceert dat het universele recht van de proefpersoon op autonome keuze (in dit geval de keuze om wel of niet als proefpersoon in onderzoek deel te nemen), kan afhangen van het oordeel van de onderzoeker en de medische ethische toetsingscommissie. Dus, hoewel er mogelijk situaties zijn waarin op inhoudelijke gronden van IC kan worden afgezien, zijn er onvoldoende redenen voor het verlaten van IC in NIS in het algemeen.

Ondanks het feit dat de argumenten voor een algemene regel voor het afzien van IC in NIS tekort schieten, is het redelijk om te denken dat de eisen die aan IC in non-interventie studies gesteld moeten worden, afwijken van de eisen in andere typen studies. Met betrekking tot de informatie die nodig is voor IC, zou in fase IV non-interventie studies in elk geval het doel van de studie en de vrijwilligheid van de proefpersoon toegelicht moeten worden. Uitleg over de opzet van het onderzoek is ook nodig, maar zaken zoals randomisatie en de weging van risico's en baten zijn meestal irrelevant of van weinig belang. Voor manier waarop IC wordt verkregen geldt dat expliciete toestemming (*opt-in)* de standaard blijft, maar dat in bijzondere situaties een geen bezwaar (*opt-out*) systeem acceptabel is. Dit geldt bijvoorbeeld wanneer *opt-in* praktisch niet haalbaar is, en in de *opt-out* procedure de informatie aan deelnemers en de vrijwilligheid van deelname gewaarborgd zijn.

In de tweede casus (**Hoofdstuk 3)** hebben we IC onderzocht in fase IV gerandomiseerde observationele geneesmiddelen studies (**P**hase **4** **R**andomised **O**bservational **D**rug **S**tudies, oftewel P4RODS). Op de site *clinicaltrials.gov* staan fase IV studies die geregistreerd als zowel 'gerandomiseerd' als 'observationeel'. Wij realiseerden ons dat de vraag naar het afzien van IC niet goed te beantwoorden is zonder de categorie 'gerandomiseerd observationeel' ter discussie te stellen. Wij gebruiken de definitie van een observationele studie van de Europese Commissie – die stelt dat in een

observationele studie de therapiekeuze niet bepaald wordt door het protocol, het voorschrijfgedrag van de arts niets beïnvloed wordt door het protocol en dat de proefpersoon niet aan extra diagnostische procedures wordt onderworpen – om duidelijk te maken dat P4RODS een contradictie is. P4RODS moet daarom zijn P4RIDS: **P**hase **4** **R**andomized **I**nterventional **D**rug **S**tudies.

Nadat we hebben vastgesteld dat P4RODS in feite P4RIDS moet zijn, kunnen we verder gaan met de vraag of IC achterwege kan blijven. Net zoals het geheel afzien van IC in fase IV non-interventie geneesmiddelenstudie (NIS) niet ethisch gerechtvaardigd is, is een dergelijke maatregel ook niet te rechtvaardigen voor P4RIDS vanwege het interventionele karakter van deze studies. Onze argumentatie tegen het achterwege laten van IC stoelt op het argument dat er sprake is van een generiek recht en door gebruik te maken van Feinberg's definitie van schade. Nu moet de vraag zijn of het afzien van IC in de specifieke situatie van P4RIDS – op inhoudelijke gronden – ethisch te rechtvaardigen is. Bij het beantwoorden van deze vraag hebben we twee potentiele inhoudelijke rechtvaardigingsgronden onderzocht: IC in P4RIDS kan achterwege blijven om redenen van publieke gezondheid; en P4RIDS kan zonder IC omdat de studie geneesmiddelen gelijkwaardig of bioequivalent zijn. Het argument dat P4RIDS geen IC behoeft omdat het bijdraagt aan publieke gezondheid is niet zomaar houdbaar omdat non-gouvernementele en quasi publieke instituties bij het onderzoek betrokken kunnen zijn. Om een trial officieel als een interventie op het gebied van publieke gezondheidszorg te kwalificeren, moet deze geleid worden door de overheid. Aangezien de meeste P4RIDS niet door de overheid worden uitgevoerd, en ze dus ook niet gezien kunnen worden als een publieke gezondheid interventie, kan een inhoudelijke rechtvaardiging ook niet worden gegeven door te verwijzen naar publieke gezondheid.

Vervolgens hebben we gekeken naar de studie geneesmiddelen, en naar de mogelijkheid dat zaken zoals gelijkwaardigheid en bioequivalentie gronden zijn voor het afzien van IC. Echter, zelfs wanneer er geen grote risico's zijn – zoals bij het vergelijken van twee bioequivalente geneesmiddelen in een P4RIDS – kunnen er klinisch relevante verschillen zijn tussen de twee middelen. Ook kunnen er onverwachte bijwerkingen zijn, vooral wanneer één van de geneesmiddelen onder studie via een verkorte procedure tot de markt is toegelaten. Daar komt bij dat er in P4RIDS altijd belangenconflicten op de loer liggen, als de studie ertoe leidt dat de arts afwijkt van de standaard zorg. Er zijn dus naar onze mening geen dwingende redenen om in het geval van P4RIDS IC achterwege te laten. Toestemming blijft dan een moreel vereiste en IC de standaard. Niettemin is een geen-bezwaarsysteem naar ons idee wel te rechtvaardigen bij P4RIDS met verwaarloosbaar risico.

In de derde casus **(Hoofdstuk 4)** onderzoeken we de noodzaak van en de manier waarop IC gevraagd moet worden voor het aanleggen van een biobank met bloed van psychiatrische patiënten voor farmacogenetisch onderzoek. Net als in de eerdere casus,

zijn we ook hier begonnen met de vraag: is het afzien van IC ethisch te rechtvaardigen? In dit geval gingen we uit van de aanname dat het uitvoeren van epidemiologisch onderzoek zonder IC alleen in uitzonderlijke gevallen kan worden toegestaan. De vraag of IC in het algemeen achterwege kan blijven is daarmee een gepasseerd station. Om te onderzoeken of het onder bepaalde omstandigheden wel mogelijk is om af te zien van IC in dit type onderzoek, hebben we gekeken naar twee veelgenoemde voorwaarden daarvoor: de risico's voor de deelnemers mogen niet meer dan minimaal zijn, en het moeten verkrijgen van IC zou het onderzoek praktisch onuitvoerbaar maken. Ten aanzien van de eerste voorwaarde redeneren wij dat gegeven de huidige situatie onvoldoende aanleiding geeft voor de claim dat de risico's minimaal zijn: sociale, psychologische en economische risico's zijn mogelijk zelfs zeer reëel. Met betrekking tot de tweede voorwaarden geldt dat in de besproken casus de patiënten niet onbereikbaar waren, waardoor 'praktische onuitvoerbaarheid' niet van toepassing is. Verder geven we als reden dat de mentale kwetsbaarheid van de betreffende groep patiënten het 'praktische' argument van ondergeschikt belang maakt. Zodoende vinden wij dat er geen gronden zijn voor het rechtvaardigen van het afzien van IC in psychiatrische biobanken voor farmacogenetisch onderzoek. Bovendien, gezien de kwetsbaarheid van de patient-proefpersonen, is alleen een opt-in procedure met ondersteuning van de potentiele proefpersoon gerechtvaardigd. Dat betekent dat ook een opt-out systeem uit beeld verdwijnt.

Deel II: Het wegen van baten en risico's

In het tweede deel doen we een stap terug. Het evalueren van risico's en baten is een ethisch vereiste voor elke klinische studie. Natuurlijk is dat ook op fase IV studies van toepassing. Niettemin waren wij van mening dat het nodig was om de vraag te stellen: "Hoe moeten beoordelaars deze evaluatie doen?" voordat we konden gaan nadenken over hoe deze evaluatie er in fase IV moet uitzien. Een voorlopige indicatie van de toepasbaarheid van de resultaten van deel II in fase IV, geven we in hoofdstuk 10.

In dit deel gaan we in op de kwestie van de noodzaak van tools voor de risico-baten evaluatie: we beoordeelden huidige benaderingen en geven aan hoe methoden uit de besliskunde kunnen bijdragen aan de evaluatie van baten en risico's; en we illustreerden hoe de besliskunde medisch ethische toetsingscommissies (METC's) kan helpen bij hun taak om baten en risico's te evalueren.

In **Hoofdstuk 5** rekenen we af met de volgende kwestie: "METC's moeten de baten en risico's van een trial beter evalueren, maar dat kost geld, is tijdrovend, moeilijk en belastend voor alle betrokkenen omdat het zou betekenen dat er meer regels en procedures moeten worden nageleefd vanwege de ethiek" (een voorbeeld van ethische inflatie). Onze argumentatie is dat dit probleem – en dus ook de ethische inflatie – vermeden kan worden als we het niet zozeer bekijken als "inflatie" maar als een kwestie van helderheid en transparantie ten aanzien van wat risico-batenanalyse is en welke instrumenten nodig zijn voor deze evaluatie. We brengen daarmee ook kort onder de

aandacht dat het evalueren van baten en risico's niet enkel een kwestie is van het geven (of krijgen) van meer gegevens. In plaats daarvan is het nodig om meer expliciet en zo systematisch mogelijk – en zo min mogelijk intuïtief – te werk te gaan bij het structureren van data en het onderbouwen van de vraag om specifieke data. Besliskunde en Risk studies zijn gepresenteerd als mogelijke bronnen voor het vinden van evaluatie instrumenten.

In **Hoofdstuk 6** evalueren we de twee belangrijkste benaderingen voor risico-batenanalyse (dit zijn de procedure-niveau benaderingen): Net Risk Test en Component Analysis. De grootste moeilijkheid voor beide benaderingen is de kans op verwarring. Daarmee bedoelen we dat de benaderingen geen onderscheid maken tussen verschillende taken: risico-batenanalyse, risico-batenevaluatie, risicobehandeling en besluitvorming. Dit gebrek aan onderscheid leidt ertoe dat beide benaderingen belastend en verwarrend kunnen zijn omdat al deze taken door één partij gedaan moeten worden: de METC.

Voor een antwoord op de verwarring hebben we gebruik gemaakt van risk studies en besliskunde om de verschillende taken te verhelderen; om duidelijk te maken wie verantwoordelijk zou moeten zijn voor de verschillende taken bij de beoordeling van een klinische studie; en hoe besliskunde en risk studies kunnen bijdragen aan het realiseren van deze taken.

Risico-batenanalyse betreft het inventariseren van risico's en baten, hun oorzaken en consequenties. Ook hoort erbij het presenteren van deze rijkdom aan informatie op een systematische en omvattende wijze, die past bij het doel waarvoor de informatie op een rij gezet moest worden. Er zijn verschillende manieren om deze analyse te verrichten, waaronder *fault tree analysis*, *event tree analysis*, *Bayesian networks, Monte Carlo simulation* enzovoorts. Omdat het erom gaat de rijkdom aan data in één beeld van de baten en risico's te vangen, pleiten wij ervoor dat de sponsor van de studie hiervoor verantwoordelijk moet zijn. Risico-bate*nevaluatie* daarentegen is het proces waarin risico's en baten vergeleken worden met gegeven criteria voor het wegen van het belang van de risico's en de baten. Hierbij kan de *multiattribute utility theory* behulpzaam zijn. Naar onze mening zou zowel de sponsor als de METC verantwoordelijk moeten zijn voor deze taak. Risicobehandeling verwijst naar het vergroten van het sociale belang van een studie, het minimaliseren van risico's voor de proefpersonen en het maximaliseren van de voordelen voor de proefpersonen. Inbreng van zowel de sponsor als de METC is nodig voor deze taak. Tenslotte behelst besluitvorming het beoordelen of –op basis van het voorgaande en gegeven de baten – het risico van een klinische studie acceptabel is. Dit is overduidelijk de taak van de METC.

Beginnend bij de taak van benefit-risk evaluatie, laten we in **Hoofdstuk 7** zien dat de multiattribute utility theory mogelijk een goed instrument is voor beoordelaars. Als deze theorie wordt gebruikt worden niet alleen de meest betrouwbare feiten expliciet

gemaakt; ook persoonlijke waarden, morele principes, intuities en deskundigen oordelen worden uitgedrukt in utility values, attribute weights en total utility scores. Explicitering van deze elementen leidt tot een beter geïnformeerd ethisch redeneren en dus tot een beter rationeel verdedigbaar besluitvormingsproces.

Deel III heeft betrekking op een essentieel kenmerk van fase IV studies, namelijk dat deze studies een therapeutische orientatie hebben. Fase IV trials zijn te onderscheiden van studies in andere fasen, juist door het postmarketing karakter van de eerste. Om beter inzicht te krijgen in de huidige stand van zaken, hebben we eerst een studie uitgevoerd naar het voorkomen van claims op bijkomende voordelen in fase IV *non-inferiority* studies (studies waarin gekeken wordt of twee behandelingen een vergelijkbare werkzaamheid hebben). Daarna hebben we de *fiduciary obligation*, ofwel de verplichting voor de arts voortkomend uit diens rol van vertrouwenspersoon, in fase IV onderzocht.

Uitgaande van de gedachte dat de waarde een fase IV trial afhangt van de klinische relevantie, hebben we in **Hoofdstuk 8** gekeken naar 41 fase IV trials en onderzocht of de auteurs in hun publicaties informatie gaven over bijkomende voordelen van het studiegeneesmiddel bovenop de claim dat de werkzaamheid van de studiebehandelingen vergelijkbaar is. In geval van een claim op bijkomende voordelen hebben we onderzocht of die in de trial bewezen werd. “Bijkomende voordelen” kunnen zijn: een beter veiligheidsprofiel van het middel, maar ook een betere toedieningsvorm, meer compliance en kosten-effectiviteit. In onze studie werd in 22 van de 41 fase IV non-inferiority trials een bijkomend voordeel geclaimd, in 10 studies werd een formele statistische analyse uitgevoerd en in slechts 1 geval was er een groepsgrootteberekening voor de claim van bijkomend voordeel. Onze conclusie is dat er ruimte is voor verbetering van de opzet van fase IV non-inferiority trials met claims op bijkomende voordelen.

In **Hoofdstuk 9** betogen we dat in de context van fase IV, arts onderzoekers hun plichten die voorkomen uit de rol van vertrouwenspersoon (hun fiduciaire verplichtingen), behouden. We doen dat door eerst aan te tonen dat het idee dat ethiek van medisch-wetenschappelijk onderzoek onderscheiden moet worden van klinische ethiek, niet toepasbaar is in fase IV. In de onderzoeksethiek is het dominante perspectief dat de ethiek van de klinische praktijk onderscheiden moet worden van de ethiek van onderzoek omdat de klinische praktijk-doelen fundamenteel verschillen van de doelen van onderzoek. Wij betogen dat dit argument niet toepasbaar is in fase IV, omdat in fase IV de studiegeneesmiddelen al tot de markt zijn toegelaten. De is daarom normaal om therapeutische effect te verwachten in deze fase.

We hebben daarna onderzocht wat een fiduciaire verplichting is. Een fiduciaire relatie is een dienstverleningsrelatie, bedoeld voor het leveren van diensten die door publiek beleid worden ondersteund. Soms kan men afzien van bepaalde fiduciaire plichten, terwijl andere een intrinsiek onderdeel zijn van de relatie. De arts-patiënt relatie is een voorbeeld van een fiduciaire relatie. Wij redeneerden dat een arts-onderzoeker

primair een arts is, wiens fiduciaire verplichting is om het welbevinden van de patiënt te bevorderen.; in het geval van (fase IV) medisch wetenschappelijk onderzoek, vraagt de arts aan de patient om toestemming voor het afzien van enkele onderdelen van de verplichting, via de IC procedure.

Tenslotte tonen we aan dat, gezien de verstrengeling van onderzoek en praktijk in fase IV, arts-onderzoekers, in samenwerking met andere onderzoekers en METC's moeten zorgen dat de opzet, methodologie en de uitvoering van een onderzoek geen afbreuk doet aan de therapeutische waarde van het onderzoek voor de patiënt-proefpersonen.

In **Hoofdstuk 10** vatten we de belangrijkste conclusies van dit proefschrift samen:

A. Als het afzien van IC ter discussie staat, is het ethisch gezien noodzakelijk om die discussies in de sfeer van mensenrechten te voeren;
B. Het feit dat er veel verschillende soorten Fase IV trials zijn, is ethisch relevant;
C. De verschillen tussen typen fase IV studies zijn een reden om kwesties als het afzien van IC, de manier waarop IC gezocht moet worden en de inhoud van het IC formulier, in ethisch opzicht verschillend te bezien;
D. De ethische evaluatie van een fase IV studie moet uitgaan van een therapeutische oriëntatie;
E. Het wegen van risico's en baten in fase IV is een gemeenschappelijke verantwoordelijkheid van de sponsor/onderzoeker en de METC;
F. Bij de weging van baten en risico's in Fase IV, uitgaande van de therapeutische oriëntatie en het gebruik van *expected utility theory* (met name de *multiattribute utility* theory), moeten enkele ethische voorwaarden in acht genomen worden:

a. De *benefit utility table* moet altijd (potentiele) "directe baten" bevatten;

b. Het gewicht van directe baten mag niet verwaarloosbaar zijn in vergelijking tot het gewicht van andere baten, zoals het voordeel voor de samenleving.

c. De *risk disutility table* moet altijd de volgende categorieën bevatten: "risico's van studiedeelname" en "risico's van de experimentele interventie".

d. In beide categorieën ("risico's van studiedeelname" en "risico's van de experimentele interventie") , moeten "belasting" en "ongemakken" (samen of apart) in overweging worden genomen.

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Ang sanaysay na ito ay isang pagbibigay-pansin sa ilang mga etikal na isyu na partikular sa ika-4 na bahagi ng pananaliksik sa gamot (ibig sabihin ay, pag-aaral sa gamot na awtorisado na) at upang magbigay ng mga paunang tugon sa mga naturang isyu. Ang mga isyung natalakay ay napapaloob sa tinatawag na tularang proteksyon (*protection paradigm*) nila van Thiel at van Delden, yuon ay ang mga isyung etikal na napananarinari ng mga katangian ng ika-4 na bahagi at hindi ng iba't-ibang kontekstong socio-ekonomiya. Siyempre, hindi namin maaaring sabihin na ang mga isyung nauukol sa makatuwirang pagbabaha-bahagi (*distributive justice*) ay mas may kaunting halaga; ang mga isyung nauukol sa makatwirang pababaha-bahagi ay kapwa kagyat at mahalaga katulad ng mga problemang napapaloob sa tularang proteksyon. Gayunpaman, dahil may konseptual na pangunguna ang mga etikal na isyung pundasyonal, at dahil ang pag-aaral na ito ay maaaring isa sa mga nauna, kung hindi man ang pinakauna na nagbigay-pansin sa pamamaraang pinalawig sa mga etikal na isyu sa ika-4 na bahagi, sa wari namiý kailangan at kapaki-pakinabang na limitahan ang ating sarili sa mga isyu sa loob ng tularan proteksyonista. Sa loob ng tularang ito, higit pa naming nilimitahan ang diskusyon sa mga isyu ukol sa pabatid pahintulot (*informed consent, IC*), pagtatasa ng mga pakinabang at panganib, at ang orientasyong panterapeutika ng ika-4 na bahagi.

Unang Bahagi: Pabatid pahintulot at ang ika-4 na bahagi

Sa loob ng isyu ng IC sa ika-4 na bahagi, tatlong usapin ang aming tiningnan: ang IC sa ika-4 na bahaging walang pakikihalong pananaliksik sa gamot; IC sa ika-4 na bahaging randomisadong obserbasyonal na pananaliksik sa gamot; at IC sa mga saykayatrikong biobank para sa pananaliksik na parmakohenetiko.

Sa unang usapin **(Kabanata 2)**, tiningnan naming ang IC ika-4 na bahaging walang pakikihalong pananaliksik sa gamot (*non-interventional drug studies, NIS*). Dahil walang napapagkasunduang nesesidad ng IC para sa mga obserbasyonal na pananaliksik sa panitikian, at wala ring nagkakatugmang etikal na mga alituntunin para sa mga obserbasyonal na pananaliksik, una naming itinanong kung kinakailangan ang IC para sa mga pananaliksik na ito, yuon ay, kung maaaring pangkalahatang talikdan ang IC para sa para sa lahat ng NIS. Upang tugunan ang tanong na ito, inilahad namin ang tatlong karaniwang argumento na ginagamit upang talikdan ang IC sa NIS: ang argumento na nauukol sa potensyal na pakinabang sa lipunan, ang argumento na ang panganib ay minimal, at ang argumento na walang makabuluhang panghihimasok sa awtonomiya.

Laban sa unang argumento, nangatwiran kami na ang argumento ay kapos sapagkat ito ay walang kaugnayan sa layunin ng IC; sa halip, ang unang argumento ay dumidiretso sa benepisyo ng pagtalikod sa IC. Ang pangalawang argumento, sa kabilang banda, ay humihipo sa sa isa sa mga layunin ng IC, ibig sabihin, yuon ay upang minimisahin ang

panganib para sa mga kalahok. Gayunpaman, ang argumentong ito ay kulang na kadahilanan para pangkalahatang talikdan ang IC. Isang bagay na sabihin na pinoproteksyunan ng IC ang mga kalahok laban sa panganib, at ibang bagay rin naman na sabihin na sapat na kadahilanan ang kawalan ng panganib upang pangkalahatang talikdan ang IC. Hindi nababawasan ang karapatan ng kalahok na magpasya para sa sarili dahil lamang wala o minimal na panganib. Para sa NIS, ang kawalan o ang minimal na panganib ay hindi makapagbibigay ng karapatan sa tagasaliksik upang itala ang kalahok nang walang pahintulot. Ang ikatlong argumento -- na nagsasaad na sa pamamagitan ng pamantayan ng makatwirang tao, walang makabuluhang panghihimasok sa awtonomiya ang nangyayari sa tuwing pangkalahatang tinatalikdan ang IC sa NIS -- ay may suliraning lohikal at moral-pangkatwiran. Sa aspetong lohikal, nabigo ang pangatlong argumento sapagkat itinutumbas nito ang ipinapalagay na pahintulot sa aktwal na pahintulot; sa aspetong moral-pangkatwiran, nagiging depende sa tagasaliksik (o sa komite ng etika) kung ano ang makatwiran at etikal sa larangan ng IC, at dahil dito, nawawala na ang totoong layunin ng iC. Sa madaling salita, bigo ang ikatlong argumento sapagkat ang panlahat na karapatan sa awtonomikong pagdedesisyon (at sa kasong ito, ang pagdedesisyon na lumahok o hindi lumahok sa pananaliksik) ay napapalitan ng paunang hatol ng tagasaliksik / komite ng etika. Samakatuwid, bagaman maaaring may partikular na mga pagkakataon kung saan ang IC ay maaaring talikdan dahil sa mga katanggap-tanggap na mga kadahilanan, walang sapat na kadahilanan para panlahat ng talikdan ang IC sa NIS.

Kahit na hindi madedepensahan ang pankalahatang pagtalikod sa IC sa NIS, may katwiran para isipin na ang nilalaman at pamamaraan ng IC sa ika-4 na bagahing NIS ay hindi pareho sa ibang pananaliksik. Sa larangan ng pahintulot, ang IC sa ika-4 na bahaging NIS ay mangangailangan ng mabuting pagpapaliwanag ng layunin ng pagasasaliksik at na likas na kusang-loob ang pagsali sa pananaliksik. Ang paliwanag sa disenyo ng pananaliksik ay kinakailangan rin; ngunit, ang mga isyu ng randomisasyon at ang balanse ng benepisyo at panganib ay maaaring walang kaugnayan o hindi importante. Sa usapin ng pamamaraan ng IC, maaaring katanggap-tanggap ang pamamaraang opt-out (ang pamamaraan kung saan ang kalahok ay isinali na, maliban na lang kung nagsabi ang kalahok na tanggalin sya sa pagsasaliksik), basta't ang proseso ay boluntaryo at nagbibigay-kabatiran sa mga kalahok.

Sa pangalawang usapin **(Kabanata 3)**, tiningnan namin ang IC sa ika-4 na bahaging randomisadong obserbasyonal na pananaliksik sa gamot (*phase IV randomized observational drug studies, P4RODS*). Sa *clinicaltrials.gov*, may mga ika-4 na bahaging pananaliksik na rehistrado bilang parehong randomisado at obserbasyonal. Naisip namin na ang tanong ukol sa pagtalikod sa IC ay hindi masasagot ng maayos hangga't hindi natin kinukwestyon ang kategoryang, "randomisadong obserbasyonal." Gamit ang depinisyon ng Europeong Komisyon ng obserbasyonal na pananaliksik, nangatwiran kami na dahil hindi maaari na sa isang obserbasyonal na pananaliksik ang terapeutika ay dinidiktahan

ang protokol, o ang reseta ay may kinalaman sa pakikilahok sa pananaliksik, o na mayroong mga karagdagang pamamaraang dyagnostiko o pangpagmamanman, ang P4RODS ay isang kasalungatan. Ang P4RODS ay nararapat na tawaging P4RIDS, yuon ay, ika-4 na bahaging randomisadong interbensyunal na pananaliksik sa gamot (*phase IV randomized interventional drug studies, P4RIDS*).

Matapos naming maipakita na ang P4RODS ay dapat tawaging P4RIDS, nagpatuloy kami sa tanong, maaari bang talikdan ang IC? Dahil hindi mabigyan ng katanggap-tanggap na etikal na pangangatwiran ang pangalahatang pagtalikod sa IC sa NIS, maaari rin nating sabihin na ang pangkalahatang pagtalikod sa IC ay hindi katanggap-tanggap sa P4RIDS sapagkat ang ganitong pananaliksik ay interbensyunal. Nangatwiran kami laban sa pangkalahatang pagtalikod sa IC gamit ang argumentong panlahat na karapatan (*generic right*) at ang kahulugan ni Feinberg ng pinsala. Dahil dito, ang katanungan dapat ay, mayroon bang etikal na katanggap-tanggap na kadahilanan ang sirkumstayal na pagtalikod sa IC sa P4RIDS? Para sagutin ang katanungang ito, tiningnan namin ang dalawang posibleng sirkumstansyal na kadahilanan para talikdan ang IC: ang IC sa P4RIDS ay maaaring talikdan sa kadahilanang pampublikong kalusugan; at ang IC sa P4RIDS ay maaaring talikdan dahil sa equipotent o bioequivalent na kalikasan ng ibang mga gamot. Na ang IC sa P4RIDS ay maaaring talikdan sa kadahilanang pampublikong kalusugan ay hindi balidong argumento dahil bagama't maaaring mabilang ang mga hindi pampubliko at mala-publikong institusyon sa mga pananaliksik na ito, para opisyal na tawaging pagsusumikap para sa pampublikong kalusugan, kinakailangan na ito ay pangunahan ng gobyerno.

Sapagkat karamihan ng P4RIDS ay hindi pampubliko, at dahil dito ay hindi maaaring ituring ang mga ito na pagsusumikap para sa pampublikong kalusugan, ang pampublikong kalusugan ay hindi ang wastong distrito para sa paghahanap ng sirkumstansyal na kadahilanan para sa pagtalikod sa IC. Sumunod ay tinignan namin ang kalikasan ng mga gamot, yuon ay, kung ang mga katangian kaparis ng equipotence o bioequivalence ay maaaring posibleng kadahilanan para sa pagtalikod sa IC. Ngunit, kahit na sa kawalan ng grabeng panganib kaparis ng sa P4RIDS sa mga gamot na bioequivalent, maaaring mayroon pang potensyal na klinikal na makabuluhang pagkakaiba ang dalawang gamot na kinukumpara, at ang mga inkombenyensiya ay maaaring asahan lalo na sa mga pagsasaliksik na nauugnay sa mga produktong "modified release". At saka, sa P4RIDS, andyan parati ang isyu ng salungat na interes sapagkat ang paglihis sa karaniwang pag-aaruga sa pasyente ay nangyayari. Dahil dito, wala kaming makitang nakakapanghimok na sirkumstansyal na kadahilanan para sa pagtalikod sa IC. Ang pahintulot ay nananatiling moral na nesesidad at IC ay syang pamantayan. Gayunpaman, ang opt-out na pamamaraan ay maaaring katanggap-tanggap para sa mga P4RIDS na may minimal na panganib.

Sa pangatlong usapin, **(Kabanata 4),** tiningnan naming ang isyu ng nesesidad at pamamaraan ng pagkuha ng IC ng mga pasyenteng sikayatriko na kung saan ang sampol ng kanilang dugo ay nakatabi sa isang sikayatrikong biobank para sa parmakohenetikong pananaliksik. Kaparis din ng mga naunang usapin, sinimulan namin ang usaping ito ng tanong, “maaari bang mabigyan ng katanggap-tanggap na etikal na kadahilanan ang pagtalikod sa IC?” Para sa usaping ito, ipinalagay namin na ang pagtalikod sa IC ay maaaring mapayagan sa ilang epidemyolohikal na pananaliksik sa mga bihirang pangyayari lamang. Dahil dito, hindi na namin kailangang tanungin kung maaaring pangkalahatang talikuran ang IC. Para maimbestigahan kung may katanggap-tanggap na kadahilanan para sa sirkumstansyal na pagtalikod sa IC para sa ganitong klaseng pananaliksik, tiningnan namin ang dalawang karaniwang binabanggit na kondisyon para sa pagtalikod: ang panganib sa mga kalahok ay hindi hihigit sa minimal; at ang pagkuha ng pahintulot ay magiging balakid para sa pagsasagawa ng pananaliksik. Hinggil sa unang kondisyon, kinatwiran namin na sa kasalukuyan, hindi natin maaaring sabihin na ang mga panganib sa mga ganitong uri ng biobank ay minimal; katunayan, ang mga panganib na panlipunan, sikolohikal, at ekonomiko ay maaaring maging tunay na mga panganib. Para sa ikalawang kondisyon, kinatwiran namin na ang mga pasyente sa ganitong kaso ay pisikal na nariyan na, at dahil dito, hindi maaaring sabihin na maaaring maging balakid ang pagkuha ng pahintulot sa pagsasagawa ng pananaliksik. Karagdagan din naming kinatwiran na dahil sa kahinaan sa kamalayan ng mga pasyenteng ito, ang kondisyon na maaaring maging balakid ang pagkuha ng pahintulot sa pananaliksik ay hindi na kasing kaimportante ng dati. Dahil dito, wala kaming makitang nakakapanghimok na sirkumstansyal na kadahilanan para sa pagtalikod sa IC para sa parmakohenetikong pananaliksik sa mga siykayatrikong biobank. Lalo pa’t ang mga pasyenteng kalahok ay may kahinaan sa kamalayan, tanging ang suportadong pamamaraan ng opt-in (kung saan ang pagiging kalahok ay nakadepende sa pahinugot ng kalahok [hindi sa pag-ayaw nito]; hindi maaaring mauna ang pagtatala ng kalahok bago ang pahinugot) ang makatarungan. Nangangahulugan din ito na ang opt-out ay hindi karapat-dapat sa ganitong klaseng pananaliksik.

Ikalawang Bahagi: Pagtimbang ng mga benepisyo at mga panganib

Ang ikalawang bahagi ay isang hakbang pabalik. Ang pagtatasa ng mga panganib at mga benepisyo ay isang etikal na pangangailangan para sa kahit anong klinikal na pananaliksik. Tiyak na nalalapat din ito sa mga pananaliksik sa ika-4 na bahagi. Ngunit, naramdaman namin na kinakailangang sagutin ang tanong, “paano dapat magtasa ang mga mangtatasa?” bago kami makapagbibigay ng mga preliminaryong pagwawari-wari sa kung paano maaaring gamitin ang pagtatasang ito sa ika-4 na bahagi. Sa Kabanata 10, Nagbigay kami ng ilang mga preliminaryong pagwawari-wari sa kagamitan ng mga resulta sa ikalawa at ikatlong bahagi ng sanaysay na ito sa ika-4 na bahagi.

Sa parteng ito, binigyan-pansin namin ang isyu na sa kasalukuyan, may pangangailangan para sa instrumento sa pagtatasa ng mga panganib at benepisyo; sinuri namin ang mga mga kasalukuyang pamamaraan at ipinabatid namin kung paano maaaring magamit ang mga pamamaraang hango sa teorya ng pagdedesisyon sa pagtatasa ng mga benepisyo at panganib; at ipinakita namin paano maaaring magamit ng komite ng etika sa pananaliksik ang teorya ng pagdedesisyon sa kanilang gawaing pagtatasa ng mga benepisyo at panganib.

Sa **Kabanata 5**, ipinakita namin na ang sumusunod na suliranin ay artipisyal, "kinakailangang mas mabuting tasahin ng mga komite ng etika sa pananaliksik ang mga panganib at benepisyo sa isang pagsasaliksik, ngunit ang paggawa nito ay hindi maiiwasang maging mas magastos, matagal, pahirap, at sagabal para sa lahat na kasangkot dahil ito ay nangangahulugan na mangangailangan na mga karagdagang alituntunin para sa kapakanan ng etika" (yuon ang tinatawag na etikal na pagpapapintog). Karagdagan naming kinatwiran na ang suliraning ito, at samaktwid ang etikal na pagpapapintog na rin, ay maaaring iwasan kung titignan natin ang isyu hindi bilang isang isyu lamang ng pagpapapintog, kung hindi isyu ng kaliwanagan at alinaw kung ano ang ibig sabihin ng pagtatasa ng panganib at benepisyo, at kung ano ang mga instrumentong maaaring kailanganin para gawain ang pagtatasang ito. Samakatwid, daglian naming ipinabatid na ang isyu sa pagtatasa ng mga benepisyo at panganib ay hindi lamang ang isyu ng pagbibigay (o pagtanggap) ng datos. Sa halip, para lagyan ng ayos ang datos at para mabigyan-kadahilanan ang paghingi ng mga espesipikong datos, kinakailangang bawasan ang pagiging kawatas at dagdagan ang pagiging malinaw at sistematiko. Ipinrisenta namin ang teorya ng pagdedesisyon at pagaaral sa panganib bilang mga posibleng pagkukunan ng mga intrumento sa pagtatasa.

Sa **Kabanata 6**, sinuri namin ang dalawang dominanteng pamamaraan ng pagtatasa ng mga benepisyo at mga panganib (yuon ang tinatawag na mga pamamaraang prosedyural na baiting): ang Pagsusuring Net Risk at ang pamamaraang Pagsusuri ng mga Bahagi. Ang pangunahing problema sa dalawang mga pamamaraan na ito ay ang kalituhan o ang kawalan ng pagkakaiba ng iba't ibang gawaing nauugnay sa benepisyo at panganib. Ang iba't ibang gawain ay ang pagaanalisa ng benepisyo at panganib, pagtatasa ng mga benepisyo at panganib, pagtalakay sa panganib, at ang pagdedesisyon. Dahil sa kakulangan ng dalawang mga natukoy na mga pamamaraan na pagiba-ibahin ang mga gawaing ito, masasabing ang dalawang pamamaraan ay nagdudulot ng kasalimuotan at kalituhan sapagkat ang iba't ibang gawain ay kinakailangang gawain ng isang lupon lamang, ang komite ng etika sa pananaliksik.

Bilang solusyon sa kalituhan, tiningnan namin ang pagaaral sa panganib at teorya sa desisyon para klaruhin kung ano-ano ang pinagkaiba ng iba't ibang mga gawain; sino ang mga responsible para sa iba't ibang gawain kapag nagtatasa ng isang klinikal na

pagsasaliksik; at paano maaaring makatulong ang teorya ng desisyon at pagaaral sa panganib sa paggawa ng mga gawaing ito.

Ang *pagaanalisa ng mga benepisyo at mga panganib* ay tumutukoy sa paglikom ng mga kaganapan, sanhi, at mga kahihinatnan na may kauganyan sa benepisyo at panganib; at ang pagpresenta ng impormasyong ito sa sistematiko at komprehensibong pamamaraan, na naaayon sa rason kung bakit binigyan ng sistema ang naturang impormasyon. May iba't ibang paraan para gawain ang pagaanalisa katulad ng fault tree analysis, event tree analysis, Bayesian networks, Monte Carlo simulation, at iba pa. Dahil ang pagaanalisa ay ang pagpresenta ng datos sa isang larawan ng mga benepisyo at mga panganib, ang sponsor ang nararapat na managot dito. Ang *pagtatasa ng mga benepisyo at mga panganib* naman ay tumutukoy sa proseso ng pagkumpara ng mga benepisyo at mga panganib laban sa pamantayan ng mga benepisyo at panganib para malaman ang kabuluhan ng mga benepisyo at ng mga panganib. Ang teorya ng maramihang katangian ng gamit (*multiattribute utility theory*) ay isa sa mga posibleng tulong sa pagtatasa. Ipinakita namin na pareho ang sponsor at ang komite ng etika sa pananaliksik ang responsable sa pagtatasa. Ang *pagtalakay sa panganib* ay ang pagdaragdag ng panlipunang halaga ng pagasasaliksik, pagbabawas ng mga panganib sa mga kalahok, at ang pagdaragdag ng mga benepisyo sa mga kalahok. Dahil dito, kinakailangang pareho ang sponsor at ang komite ng etika sa pananaliksik ang mananagot dito. Panghuli, ang *pagdedesisyon* ay ang paghusga kung, base sa mga naunang mga gawain at sa mga benepisyo ng pagaaral, katanggap-tanggap ba ang mga panganib ng pagsasaliksik. Ang pagdedesisyon ay gawain ng komite ng etika sa pananaliksik lamang.

Ang **Kabanata 7** ay nagbigay pansin sa gawaing pagtatasa ng mga benepisyo at mga panganib. Ipinakita namin sa kabanatang ito paano makakatulong ang teorya ng maramihang katangian ng gamit sa mga tagatasa. Sa teoryang ito, hindi lamang ang mga probabilidad at mga katotohanan tungkol sa pagsasaliksik ang ginagawang malinaw; ang mga personal na pagpapahalaga, mga prinsipyong moral, mga kawatasan, at mga opinyon ng eksperto ay pinapalinaw din sa pamamagitan ng kwenta ng pagpapahalaga, timbang ng mga katangian, at kabuuang puntos ng pagpapahalaga. Ang pagpapalinaw ng mga ito sa pamamagitan ng teorya sa desisyon ay nakakatulong para gawaing mas mabuti ang kaalaman ng mga nagtatasa sa kanilang pagdedesisyon at paghuhusga, at dahil dito ay nakakatulong ang pagpapalinaw na ito na gawaing mas makatwirang maipagtatanggol ang proseso ng pagdedesisyon.

Ikatlong Bahagi: Orientasyong terapeutika ng ika-4 na bahagi

Ang ikatlong bahagi ay ukol sa likas na katangian ng mga pagsasalik sa ika-4 na bahahi, yuon ay ang orientasyong terapeutiko ng mga pagsasaliksik na ito. Naiiba ang mga pagsasaliksik sa ika-4 na bahagi kumpara sa mga pagasasaliksik sa ibang mga bahagi sapagkat ang mga pagsasaliksik sa ika-4 na bahahi ay nangyayari matapos ang

awtorisasyon. Para malaman ang kasalukuyang kalagayan ng ika-4 na bahagi, una naming tiningnan kung mayroong pahayag ng karagdagang benepisyo sa mga ika-4 na bahaging pagsasaliksik na nagpapatunay ng kawalan ng kahinaan ng klase (*non-inferiority*) ng isang gamot kumpara sa isa pang gamot o placebo. Pagkatapos nito, ipinaliwanag namin ang pananagutan ng pinagkatiwalaan (*fiduciary obligation*) ng manggagamot na nagsasaliksik sa ika-4 na bahagi.

Ipinapalagay na ang halaga ng pagsasaliksik sa ika-4 na bahagi ay nakasalalay sa kaugnayan nito sa klinika. Sa **Kabanata 8**, sinuri namin ang 41 pagsasaliksik sa ika-4 na bahagi at tiningnan kung nagpahayag ang mga may-akda ng anumang karagdagang mga benepisyo bukod pa sa pagpapatunay ng kawalan ng kahinaan ng klase ng isang gamot, at kung ang karagdagang benepisyo ay napatunayan sa pananaliksik. Ang mga karagdagang mga benepisyo ay maaaring tumukoy sa mas pinabuting kaligtasan, pina-iging paraan ng paginom ng gamot, mas pinabuting pagtalima, at mas epektibong paggastos. Sa lahat ng mga natingnan na pananaliksik, 22 ang nagpahayag ng karagdagang benepisyo, 10 ang gumamit ng istatistikang pamamaraan ng pagaanalisa, at isa lamang ang nagkalkula ng laki ng sampol para sa ipinahayag na karagdagang benepisyo. Dahil dito, masasabi naming dapat pang pagbutihin ang pagdedesenyo ng mga pagsasaliksik sa ika-4 na bahagi na nagpapatunay ng kawalan ng kahinaan na nagpapahayag ng karagdagang benepisyo.

Sa **Kabanata 9**, ipinakita namin na sa konteksto ng ika-4 na bahagi, nananatili ang pananagutan ng pinagkatiwalaan ng manggagamot na nananaliksik sa kanilang mga pasyenteng kalahok sa pagsasaliksik. Para mapatunayan ito, ipinakita muna namin na ang perspektibong dapat ibahin ang etika ng pananaliksik sa etika ng klinika ay hindi naaangkop sa ika-4 na bahagi. Sa etika ng pananaliksik, mayroong nangingibabaw na perspektibo na ang etika ng klinika ay kinakailangang ibahin sa etika ng panaliksik sapagkat nagkaiba ang mga ito sa kanilang mga layunin. Ikinatwiran namin na ang argumentong ito ay hindi nauukol sa ika-4 na bahagi sapagkat ang mga sinasaliksik na mga gamot ay awtorisado na. Dahil dito, ang elementong terapeutika ay likas na inaasahan sa bahaging ito.

Sumunod ay ipinaliwanag namin kung ano ang ibig sabihin ng pananagutan ng pinagkatiwalaan. Ang relasyon ng pinagkatiwalaan sa nagtitiwala ay isang sebisyong relasyong para sa pagbibigay ng serbisyo na hinihikayat ng pampublikong patakaran. Ang ibang pananagutan ng pinagkatiwalaan ay maaaring talikdan; ngunit, ang ibang pananagutan ay likas sa relasyon. Ang relasyon ng manggagamot sa pasyente ay isang halimbawa ng relasyong ito. Ipinakita namin na ang mangagamot na nananaliksik una sa lahat ay manggagamot: ang kanyang pangunahing pananagutan ay ang pangalagaan ang kapakanan ng pasyente. Sa pananaliksik sa ika-4 na bahagi, maaari nyang hilingin sa pasyente na talikdan ang ibang aspeto ng kanyang pananagutan sa pamamagitan ng proseso ng IC.

Panghuli, ipinapalagay ang pagkapulupot ng pananaliksik sa klinika sa ika-4 na bahagi, ipinakita namin na kinakailangang siguruhin na hindi nabawasan ang halagang terapeutika ng pananaliksik (sa pamamagitan ng disenyo ng pananaliksik, pamamaraan, at kaugalian sa pananaliksik) para sa mga pasyente ng mga manggagamot, sa pakikipagtulungan ng iba pang mga mananaliksik, mga imbestigador, at ng mga komite ng etika sa pananaliksik.

Sa **Kabanata 10**, ibinuod namin ang mga pangunahing natuklasan sa sanaysay na ito:

A. Nesesidad pang-etika ang paglalagay sa larangan ng karapatang pantao ang ano mang diskusyon ukol sa pagtalikod sa IC;

B. May kabuluhang pang-etika ang katotohanan na may iba-ibang klaseng ika-4 na bahaging pananaliksik;

C. Ang pagkakaiba-iba ng mga tipo ng pagsasaliksik sa ika-4 na bahagi ay nangangahulugan ng pagkakaiba-iba rin ng etikal na pagtalakay sa mga isyu ng pagtalikod sa IC, pamamaraan ng pagkuha ng IC, at ang mga nilalaman ng mga pormas para sa IC;

D. Kinakailangang ipalagay ang orientasyong terapeutiko sa etikang pagtasa ng ika-4 na bahagi;

E.Parehong responsibilidad ng sponsor/imbestigador at ng komite ng etika sa pananaliksik ang pagtimbang ng mga panganib at mga benepisyo;

F. Sa pagbalanse ng mga panganib at mga benepisyo sa ika-4 na bahagi, ipinapalagay ang orientasyong terapeutika at ginagamit ang teorya ng inaasahang gamit (*expected utility theory*, particular ang teorya ng maramihang katangian ng gamit), dapat tandaan ang mga sumusunod:

a. Kinakailangang isama ang (potensyal) na “direktang benepisyo” sa mesa ng mga benepisyo;

b. Hindi maaaring bale-wala ang “direktang benepisyo” kumpara sa iba pang mga benepisyo, katulad ng mga “benepisyo sa lipunan”;

c.Kinakailangang isali ang mga kategoryang “panganib dahil sa paglahok sa pagsasaliksik” at “panganib dahil sa mga gamot na sinasaliksik” sa mesa ng mga panganib;

d. Sa parehong kategorya (yuon ay, “panganib dahil sa paglahok sa pagsasaliksik” at “panganib dahil sa mga gamot na sinasaliksik), ang mga “pampabigat” at mga “abala” (maging magkasama o magkahiwalay) ay kinakailangang isaalang-alang.

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"¿Qué amor no ha vuelto?" *-- Manuel Bernabé y Hernández*

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CURRICULUM VITAE

Rosemarie Bernabe was born in the 10th of December 1975 in Parañaque Rizal, the Philippines. Her parents are Sally dela Cruz and Patricio Bernabe.

In 1998, she graduated with a degree in Bachelor of Arts in Humanities with specialization in Philosophy, *magna cum laude*, from the University of Asia and the Pacific (Philippines). Her undergraduate thesis, which garnered a perfect score, was entitled, "Dignity of man as the basis of the dignity of work in *Laborem exercens* as inspired by Thomistic philosophy."

Right after graduation, she joined the academia as a junior instructor of philosophy, first in the University of Asia and the Pacific and after 2002, in other colleges and universities in the Philippines such as the University of La Salette Collegiate Seminary, Don Bosco Collegiate Seminary, Assumption College, San Beda College, and the Ateneo University. In these institutions, she taught various philosophy subjects such as Introduction to Philosophy, Ancient Philosophy, Medieval Philosophy, Modern Philosophy, Contemporary Philosophy, Philosophy of the Social Sciences, Logic, General Ethics, Applied Ethics, Metaphysics, Filipino Philosophy, Asian Philosophy, Philosophy of the Family, and Social Institutions and Ideologies.

She struggled to combine teaching with graduate studies until 2005, when she was granted the Erasmus Mundus Scholarship. From 2005 to 2006, she attended the Masters in Applied Ethics course both in Linköping University (Sweden) and in Utrecht University. Her master's thesis was entitled, "An investigation on the Aristotelian foundations of Martha Nussbaum's Capabilities Approach and the disability issue utilizing Nussbaum's earlier works on Aristotle."

In 2006, she went back to the Philippines to continue teaching, and in 2007, her thesis was nominated for and won the Best Masters' Thesis Prize of the School of Humanities of Utrecht University.

She began with her PhD project in 2008 at the Julius Center for Health Sciences and Primary Care, Utrecht University Medical Center, the thesis of which is this book. She currently works in the Julius Center.

She and her partner Love live with their two sons in Utrecht.